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The Alkaline Degradation of 1,5-Anhydro-2,3,6-Tri-O-Methyl-Cellobiitol

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THE ALKALINE DEGRADATION OF 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL

A thesis submitted by

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SUMMARY

The degradation of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol was investigated in oxygen-free sodium hydroxide (0.5-2.5N) at 150-180°C. Cleavage of the glucosyl-oxygen bond was dominant (80-97%), while oxygen-aglycone bond cleavage accounted for the remaining 3-20%. Pseudo-first-order kinetics were employed to describe the system, for the concentration of hydroxide ion was maintained at a level greatly in excess to that of the reactant.

Apparent thermodynamic functions of activation were determined for glucosyl-oxygen bond cleavage in 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol in 2.5N sodium hydroxide. The values obtained for the enthalpy and entropy of activation (35.5 kcal/mole and -3.2 e.u., respectively) compared favorably with the values found for the degradation of 1,6-anhydro-β-D-glucopyranose (32.8 and -3.8), which has been postulated to react via an $S_N1cB(2)$ mechanism under similar conditions.

A five fold increase in the ionic strength at a constant hydroxide ion concentration resulted in a 19.5% decrease in the pseudo-first-order rate constant for glucosyl-oxygen bond cleavage (a negative salt effect). This is consistent with an $S_N1cB(2')$ mechanism and similar to the 19.3% decrease observed under comparable conditions for 1,6-anhydro-β-D-glucopyranose.

Pseudo-first-order rate constants for glucosyl-oxygen bond cleavage were determined as a function of hydroxide ion concentration at constant ionic strength. The data was consistent with an $S_N1cB(2')$ mechanism as demonstrated by the linear nature of a plot of 1/rate constant *vs.* 1/[OH-], and analysis of the values obtained for the slope and the intercept of the line.

The importance of ionization at the C-2' hydroxyl group, the first step in the $S_N1cB(2')$ mechanism, was demonstrated by subjecting 1,5-anhydro-2,3,6,2',3'-penta-O-methyl-cellobiitol to the reaction conditions. Glucosyl-oxygen bond

cleavage in the penta-methyl derivative proceeded at a rate 97% slower than glucosyl-oxygen bond cleavage in 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol.

Therefore, based on the experimental evidence, all of which is consistent with the postulated mechanism, an $S_N1cB(2')$ mechanism is proposed for the glucosyl-oxygen bond cleavage in 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol.

The presence of the methoxyl groups on the aglycone precludes a conjugate base mechanism for oxygen-aglycone bond cleavage in 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol. Also, the expected product from an S_N2 reaction for oxygen-aglycone bond cleavage, 1,5-anhydro-2,3,6-tri-O-methyl-D-galactitol, was not formed in more than trace quantities. In addition the similarities in the pseudo-first-order rate constants for oxygen-aglycone bond cleavage in this compound and those for the analogous cleavage in 1,5-anhydrocellobiitol, concluded to degrade via an S_N1 mechanism, supports the conclusion that oxygen-aglycone bond cleavage in 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol occurs via an S_N1 mechanism as well.

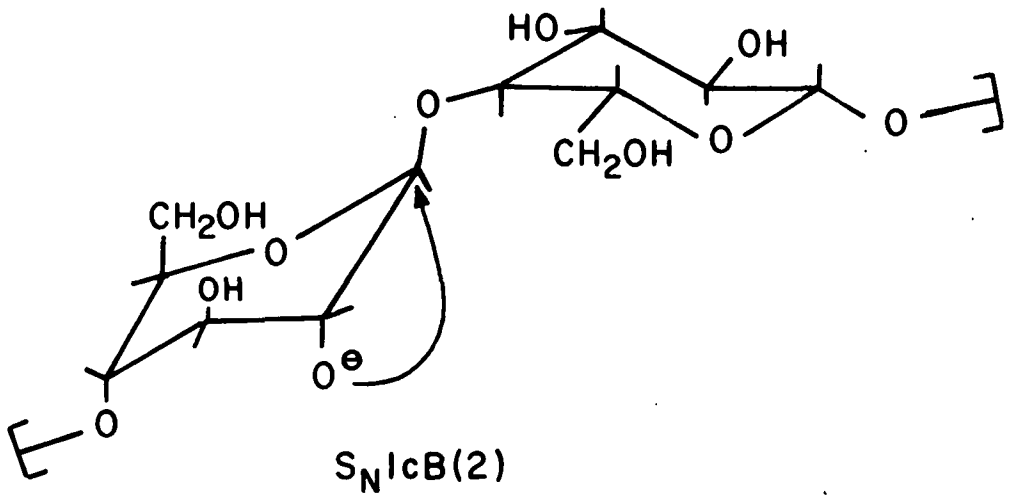
INTRODUCTION

Two general pathways for alkaline degradation of polysaccharides have been recognized for some time. Briefly, they are the sequential elimination of monosaccharide units from the reducing end of the polymer chain (peeling), and the random cleavage of glycosidic bonds, which results in a substantial decrease in the average chain length and forms new reducing end groups for subsequent peeling.

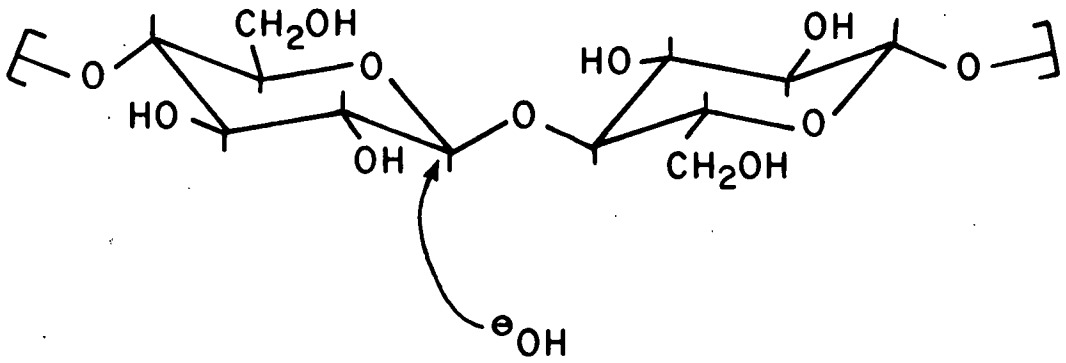
Considerable research has been done in the area of glycosidic bond degradation, and the literature has been extensively reviewed (1-5).

It has been indicated (6) that carbohydrate losses associated with the cleavage of glycosidic bonds of wood polysaccharides during a kraft cook are not as severe as previously thought. However, the degree of polymerization of the cellulose is decreased significantly, and approximately 3% of the total cellulose content is lost through such cleavage and subsequent peeling (6).

The two mechanisms generally proposed for glycosidic bond cleavage of cellulose in oxygen-free alkaline media are the neighboring group mechanism [$S_N1cB(2)$] (7-9) and nucleophilic attack by hydroxide ion at the anomeric carbon (S_N2) (10). The $S_N1cB(2)$ mechanism is analogous to that proposed by McCloskey and Coleman to account for the degradation of phenyl *trans* 1,2-β-D-glycosides (11), and which has been subsequently extrapolated, albeit questionably (1) to alkyl *trans* 1,2-β-D-glycosides. The alkaline degradation of methyl β-D-glucopyranoside and methyl β-cellobioside have also been postulated to occur via this mechanism (12). Further support for this conclusion was offered by Lai's (13) analysis of the hydroxide dependence data for the degradations of the methyl glycosides.

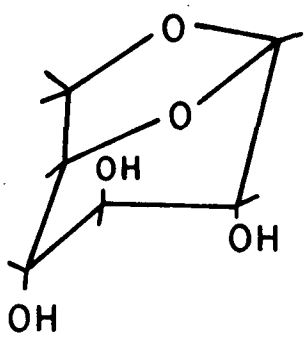


$S_N1cB(2)$



S_N2

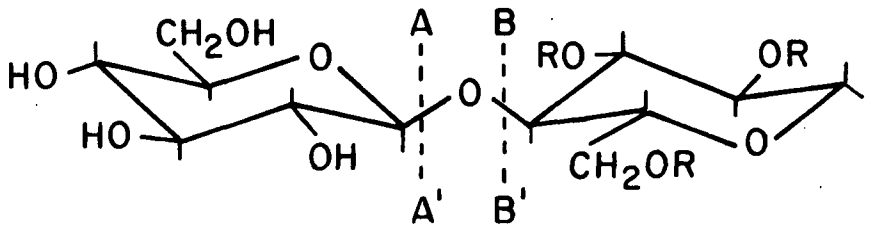
Reaction of phenyl β-D-glucopyranoside in 1.3N NaOH at 100°C resulted in an 88% isolated yield of 1,6-anhydro-β-D-glucopyranose (I) (11). Consequently, the formation of 1,6-anhydro-β-pyranoses from trans 1,2-β-glycosides has been taken as an indication of the $S_N1cB(2)$ mechanism.



I

Brandon, et al. (4,14) have studied the oxygen-free, alkaline degradation of 1,5-anhydro-4-O-(β-D-glucopyranosyl)-D-glucitol (1,5-anhydrocellobiitol) (II), and to a lesser extent, 1,5-anhydro-4-O-(β-D-glucopyranosyl)-2,3,6-tri-O-methyl-D-glucitol (1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol) (III) at temperatures ranging from 160-180°C. These relatively simple, nonreducing, cellulose model compounds were chosen for several reasons. Formation of the anhydroalditol end group prohibited the peeling reaction. In addition, the synthetic and analytical procedures were less complicated than they would have been for an oligo- or polysaccharide of longer chain length.

In aqueous sodium hydroxide solutions (0.5-2.5N) the cleavage of the glycosidic linkage in 1,5-anhydrocellobiitol (II) occurred on both sides

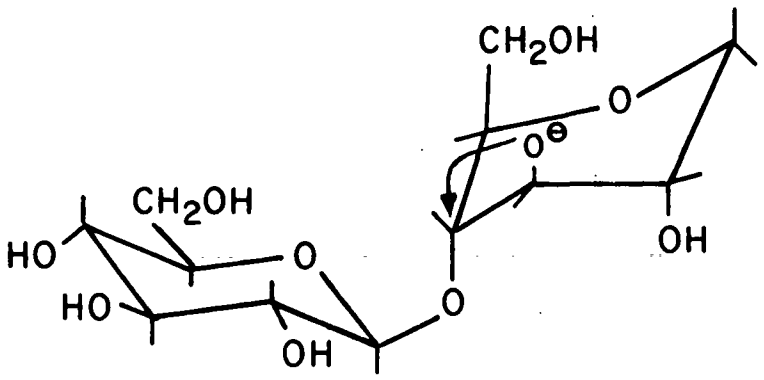


II, R = H

III, R = CH_3

of the oxygen atom (14). Cleavage of the glucosyl-oxygen bond (A-A') dominated, accounting for approximately 80-90% of the degradation, while the oxygen-aglycone bond (B-B') cleaved the remaining 10-20% of the time.

1,5:3,6-Dianhydro-D-galactitol and unidentified products, thought to be fragments and acidic compounds, resulted from the aglycone on cleavage of the oxygen-aglycone bond in 1,5-anhydrocellobiitol (II). The possibility of an S_N2 mechanism operating in this case was ruled out, for the expected product, 1,5-anhydro-D-galactitol, was only formed in trace amounts. Cleavage of the oxygen-aglycone bond in 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol (III), under the same conditions, yielded unidentified products exclusively from the aglycone. It is unlikely that a $S_N1cB(3)$ neighboring group mechanism was operating with the methylated derivative (III), as the presence of the methyl ethers prevented ionization of the hydroxyl groups on the aglycone. Therefore, since the rate constants for oxygen-aglycone cleavage in (II) and (III) were found to be essentially the



$S_N1cB(3)$

same, it was concluded that an S_N1 mechanism governed the oxygen-aglycone cleavage in (II) (14). In addition, the S_N1 mechanism for oxygen-aglycone cleavage in (II)

was supported by a high enthalpy of activation (ca. 42 kcal/mole), an increase in the pseudo-first-order rate constant with increasing ionic strength of the solution, and a decrease in the pseudo-first-order rate constant as the hydroxide ion concentration was increased.

Cleavage of the glucosyl-oxygen bond in 1,5-anhydrocellobiitol (II) resulted in formation of 1,5-anhydro-D-glucitol, exclusively from the aglycone, and partial formation of 1,6-anhydro-β-D-glucopyranose (I) from the glucosyl moiety (14). 1,5-Anhydro-D-glucitol was stable at the reaction conditions, while (I) degraded further. Fortunately, the degradation of 1,6-anhydro-β-D-glucopyranose (I) at these conditions was studied separately (14), and subsequently in greater detail (5). These data allowed the mole fraction of the degradation proceeding via formation of (I) to be calculated from the observed concentration of this reactive intermediate. Table I summarizes the percentage of glucosyl-oxygen bond cleavage in (II) and (III) resulting in the formation of (I).

TABLE I

MOLE FRACTION OF 1,6-ANHYDRO-β-D-GLUCOPYRANOSE RESULTING FROM CLEAVAGE OF THE GLUCOSYL-OXYGEN BOND OF CELLULOSIC MODEL COMPOUNDS IN AQUEOUS ALKALI AT 170°C (14)

NaOH, N	NaOTs,[a] N	1,5-Anhydro-cellobiitol (II)	1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol (III)
2.5	0.0	0.35	0.73
1.5	1.0	0.36	0.85
1.0	1.5	0.36	Not determined
0.5	2.0	0.32	0.63

[a] p-Toluene sulfonic acid, sodium salt

Based on the amounts of 1,6-anhydro-β-D-glucopyranose (I) formed from the glucosyl-oxygen bond cleavage of (II) and (III), it is apparent that there is a difference in the two reactions. Brandon, et al. (14) postulated that the predominant mechanism governing glucosyl-oxygen bond cleavage of the partially methylated derivative (III) was of the neighboring group type [$S_N1cB(2')$]. Due to the fact that lower amounts of (I) were found in the reactions with (II), it was concluded that the degradation of the glucosyl-oxygen bond of (II) was governed by a mixed mechanism, having some S_N1 character, as well as, $S_N1cB(2')$.

Consequently, the purpose of this thesis was to elucidate the mechanism of oxygen-free, alkaline degradation of 1,5-anhydro-4-O-(β-D-glucopyranosyl)- 2,3,6-tri-O-methyl-D-glucitol (III), with the primary emphasis on the mechanism of glucosyl oxygen bond cleavage. Since this bond has been postulated to cleave via the $S_N1cB(2')$ mechanism (14) the degradation of a derivative with the C-2' hydroxyl group blocked by formation of a methyl ether was also studied.

POTENTIAL MECHANISMS

GLUCOSYL-OXYGEN BOND CLEAVAGE

INTRODUCTION

A previous study (4) showed that the reaction of 1,5-anhydro-4-O-(β-D-glucopyranosyl)-2,3,6-tri-O-methyl-D-glucitol, hereafter referred to as 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol (III), in oxygen-free sodium hydroxide did not have an induction period. Also, the unmethylated derivative (II) exhibited media dependencies characteristic of ionic reactions. Therefore, it was considered improbable that a free radical mechanism was operating in this system. The ionic reaction pathways evaluated as potential mechanisms for the oxygen-free alkaline degradation of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol were: unimolecular substitution by the conjugate base of a neighboring group (S_N1cB), unimolecular nucleophilic substitution (S_N1), and bimolecular nucleophilic substitution (S_N2).

$S_N1cB(2')$ MECHANISM

The $S_N1cB(2')$ pathway for the cleavage of the glucosyl-oxygen bond of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol (III) is illustrated in Fig. 1. The first step in the conjugate base mechanism would be reversible ionization of the C-2' hydroxyl group. This would be followed by the rate-determining nucleophilic displacement of the aglycone by the C-2' oxyanion. The immediate products would be the conjugate base of 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol (IV) and 1,2-anhydro-α-D-glucopyranose (V). The 1,2-anhydride (V) could react via nucleophilic attack at C-1 by the C-6 oxyanion to form 1,6-anhydro-β-D-glucopyranose (I), or with either hydroxide ion, or water, to form D-glucopyranose (VI), which would degrade quickly at the reaction conditions. 1,6-Anhydro-β-D-glucopyranose (I) is also unstable at the reaction conditions (4,5). However, it degrades at a much slower rate than

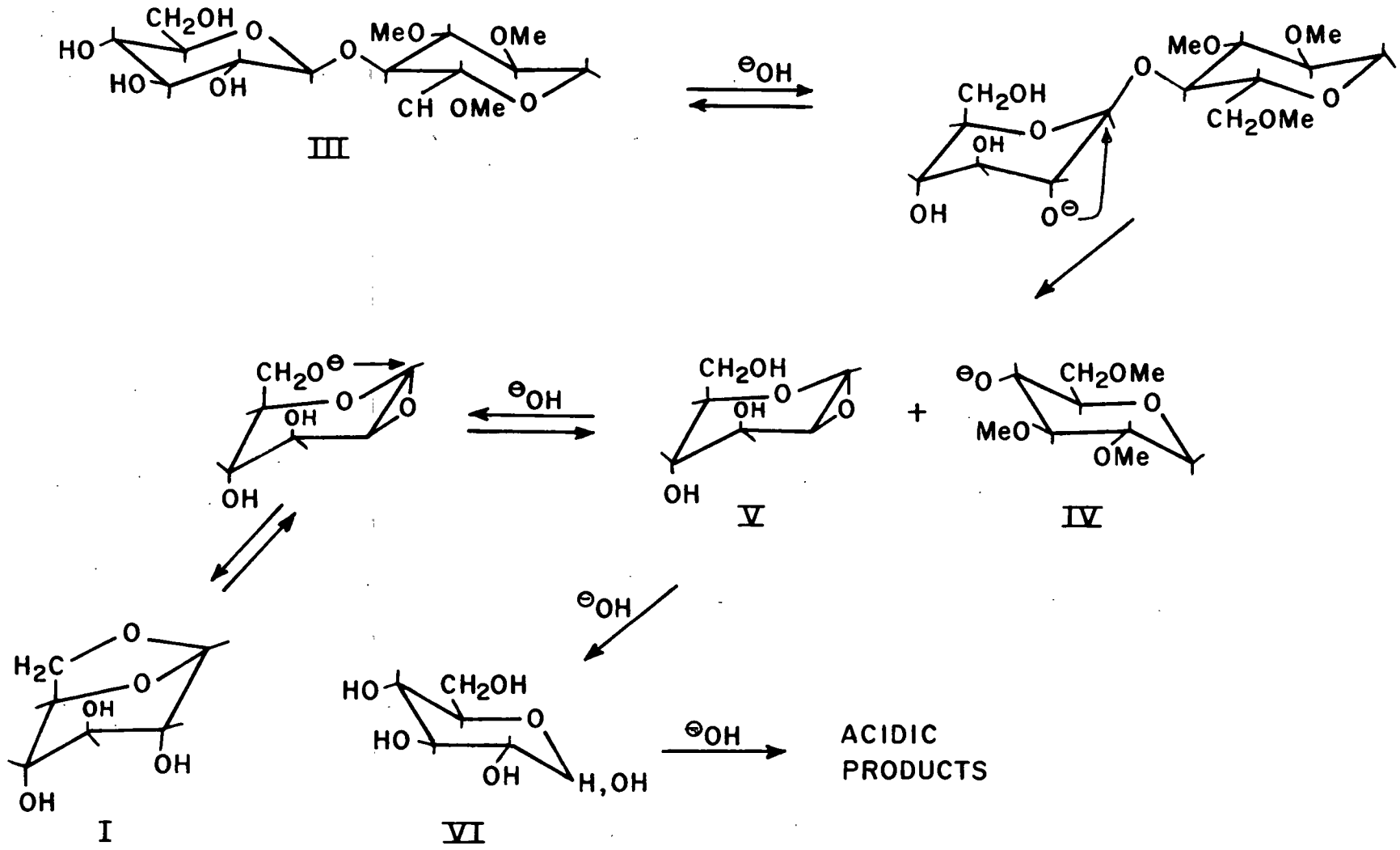


Figure 1. Potential $S_N1cB(2')$ Mechanism for Cleavage of the Glucosyl-Oxygen Bond in 1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol

D-glucopyranose (VI). It is also possible that the epoxide ring of the intermediate 1,2-anhydride (V) could migrate. Opening of the epoxide ring by the C-3 oxyanion would form another epoxide, 2,3-anhydro-D-mannopyranose. Subsequent opening of the 2,3-epoxide by the C-4 oxyanion would yield 3,4-anhydro-D-altropyranose. In order to reverse the migration, the sugar molecule must reassume the C_4^1 conformation. However, once the epoxide ring has shifted for the first time, a reducing sugar would be formed, which would rapidly degrade to acidic products. If the $S_N1cB(2')$ mechanism is governing the cleavage of the glucosyl-oxygen bond, significant quantities of 1,6-anhydro-β-D-glucopyranose (I) would be expected, since formation of (I) has been taken as an indication of the $S_N1cB(2)$ mechanism in other β-glycosides (11).

S_N1 MECHANISM

The potential S_N1 mechanism for glucosyl-oxygen bond cleavage in (III) is presented in Fig. 2. Heterolysis of the glucosyl-oxygen bond would produce the conjugate base of 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol (IV) and the D-glucopyranosyl cation (VII). The cation (VII) could form D-glucose by reaction with hydroxide ion, or undergo intramolecular reactions to form 1,6-anhydro-β-D-glucopyranose (I), or 1,2-anhydro-α-D-glucopyranose (V).

S_N2 MECHANISM

The S_N2 mechanism is a one-step reaction in which one nucleophile is displaced by another. The reaction proceeds with inversion of configuration at the reactive site, since the formation of the "new" bond occurs simultaneously with cleavage of the "old" bond. If the reactive site is an asymmetric carbon, and the resulting product is isolable, the inversion of configuration is easily discerned. Also, the rate of reaction is proportional to the strength (nucleophilicity) of the attacking nucleophile.

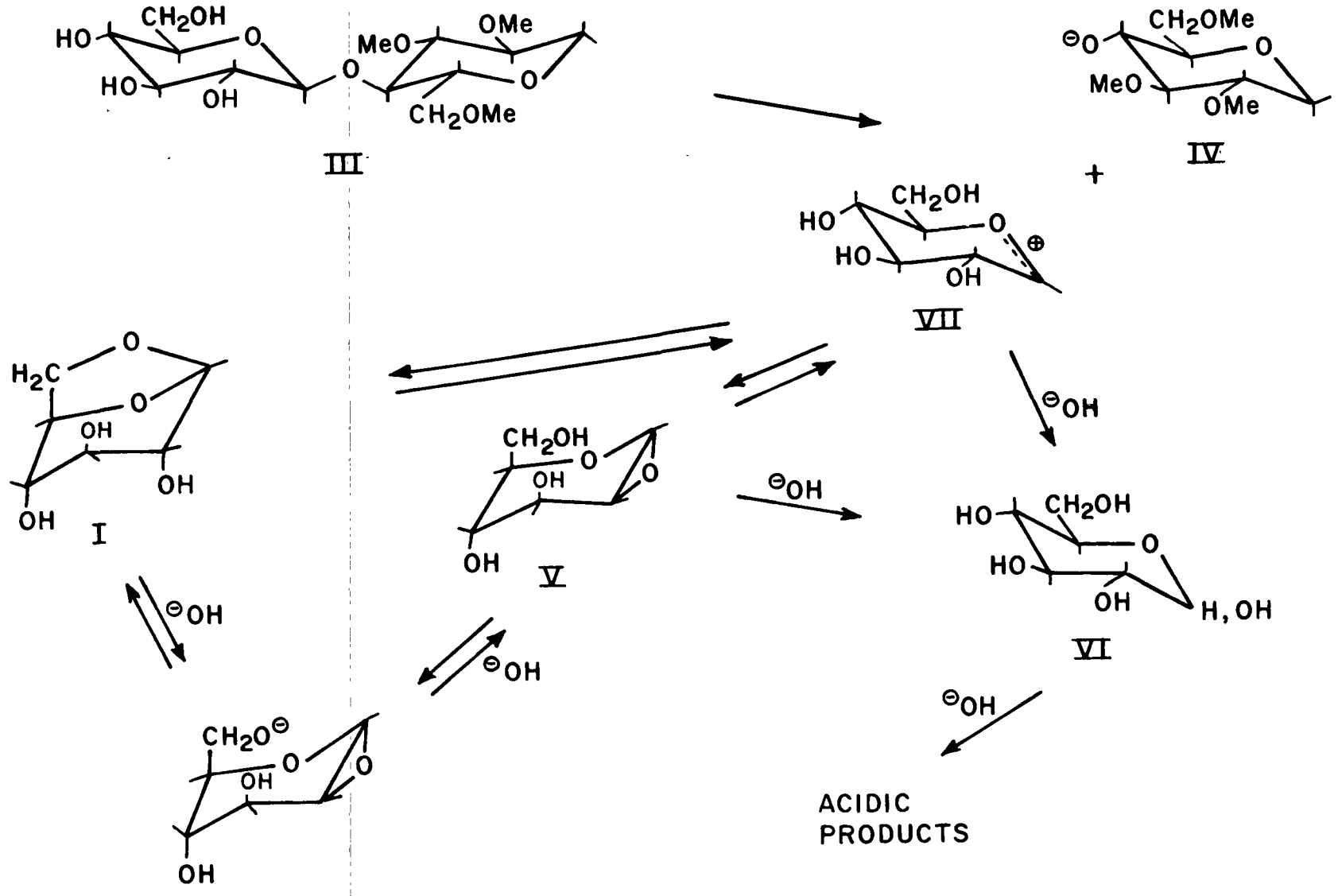


Figure 2. Potential S_N1 Mechanism for Cleavage of the Glucosyl-Oxygen Bond in 1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol

The possibility of an S_N2 mechanism for the glucosyl-oxygen bond cleavage of 1,5-anhydrocellobiitol (II) was discounted (14), since replacement of hydroxide ion by iodide ion, considered to be a stronger nucleophile based on room temperature data, as the attacking species did not result in an increase in the reaction rate. This conclusion may not be valid, for it has been indicated that using iodide ion as a probe for the S_N2 mechanism is not conclusive at higher temperatures (5).

Consequently, the S_N2 mechanism was considered as a possibility for glucosyl-oxygen cleavage in this work. This pathway is illustrated in Fig. 3. Again the sole product from the aglycone would be the conjugate base of 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol (IV). Attack by hydroxide ion at C-1' would result in exclusive formation of α-D-glucopyranose, which would degrade quickly at the reaction conditions. Therefore, formation of 1,6-anhydro-β-D-glucopyranose would not occur in an S_N2 reaction.

$S_N1cB(4')$ MECHANISM

An $S_N1cB(4)$ mechanism has been proposed for the alkaline degradation of phenyl β-D-mannopyranoside (1). However, this mechanism was not considered as a possibility in this system. In a related reaction, when the C-2 hydroxyl group of p-nitrophenyl β-D-xylopyranoside was methylated the rate of its alkaline degradation decreased by a factor of 1000. More importantly, the reaction mechanism shifted to bimolecular nucleophilic aromatic substitution, rather than to $S_N1cB(4)$ (15).

OXYGEN-AGLYCONE BOND CLEAVAGE

NEIGHBORING GROUP MECHANISMS

The presence of the methyl groups in 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol (III) preclude ionization of any of the hydroxyl groups on the aglycone. Thus, no conjugate base mechanisms are possible for oxygen-aglycone bond cleavage.

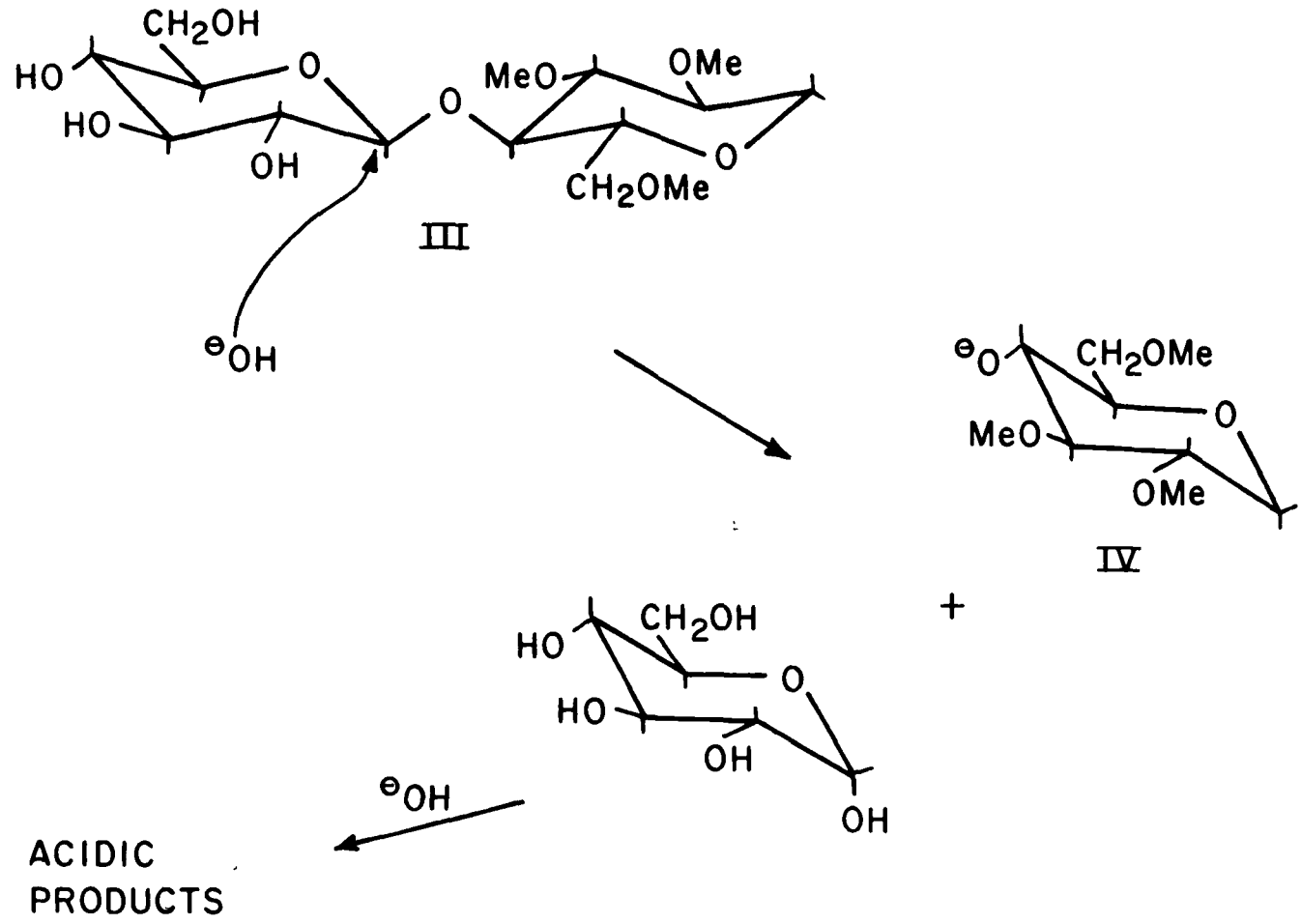


Figure 3. Potential S_N2 Mechanism for Cleavage of the Glucosyl-oxygen Bond in 1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol

S_N2 MECHANISM

The potential S_N2 pathway for oxygen-aglycone cleavage of (III) is presented in Fig. 4. The attacking hydroxide ion would invert the configuration at C-4, resulting in the formation of 1,5-anhydro-2,3,6-tri-O-methyl-D-galactitol (VIII) as the sole product from the aglycone, and the glucopyranosyloxy anion (IX) from the glucosyl moiety. The anion (IX) would degrade to acidic products quickly at the reaction conditions.

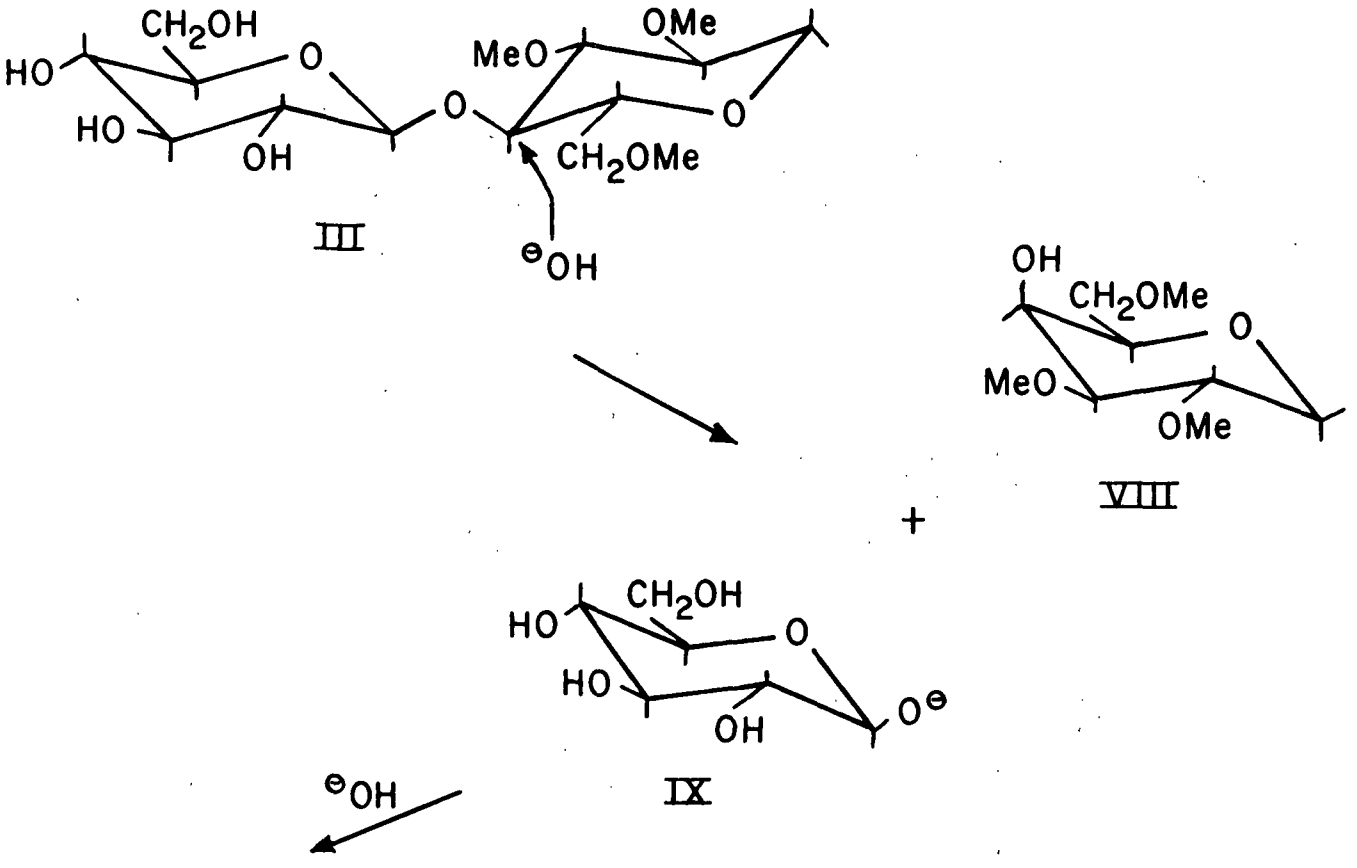


Figure 4. Potential S_N2 Mechanism for Oxygen-aglycone Bond Cleavage in 1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol

S_N1 MECHANISM

Figure 5 illustrates the potential S_N1 mechanism for oxygen-aglycone cleavage of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol (III). Heterolysis would yield the unstable glucopyranosyloxy anion (IX) and the 1,5-anhydro-2,3,6-tri-O-methyl-4-deoxy-D-xylohexitol-4-cation (X). The cation (X) could rearrange to a more stable ion (XI) and from there to a hemiketal (XII), which would subsequently fragment.

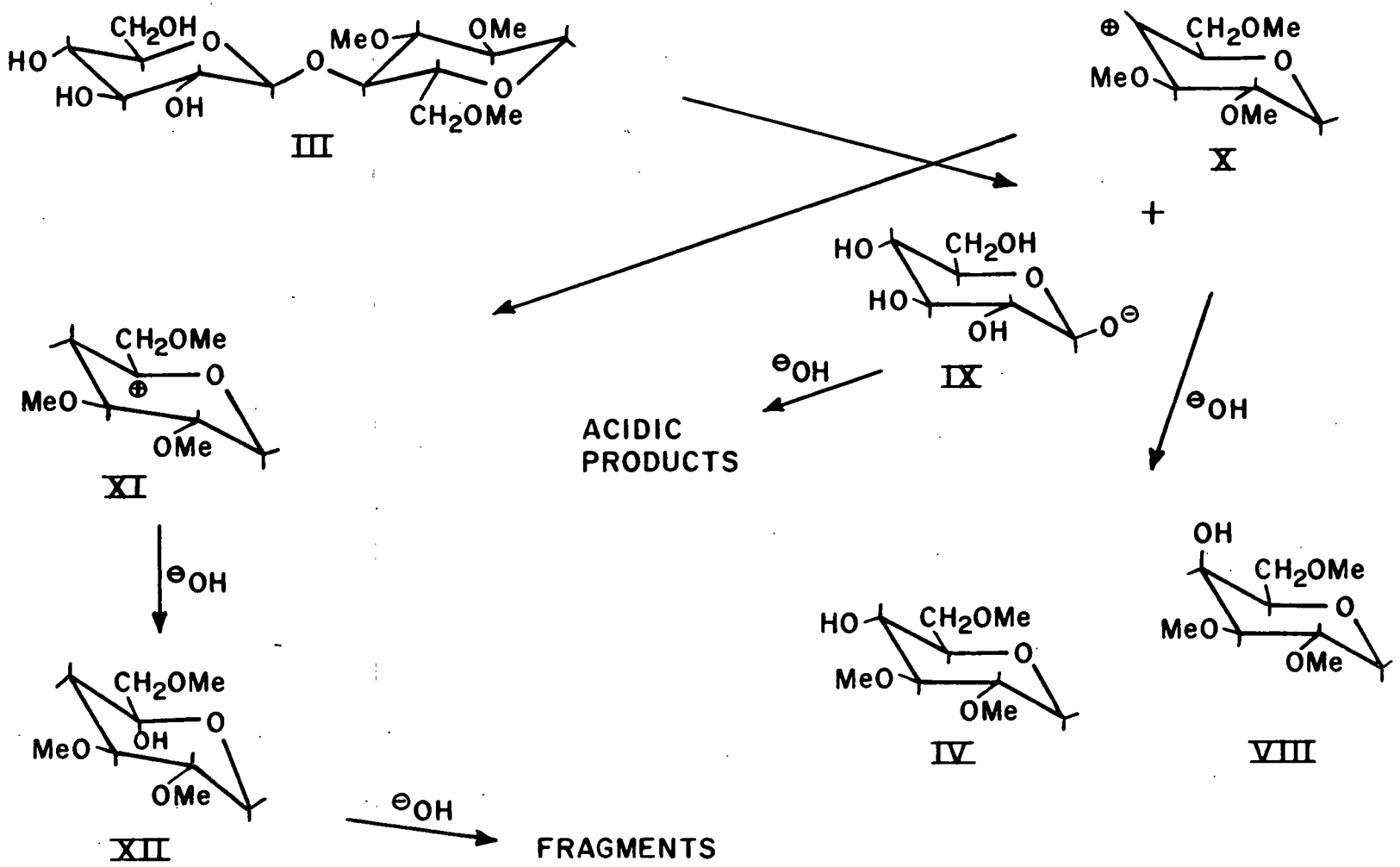
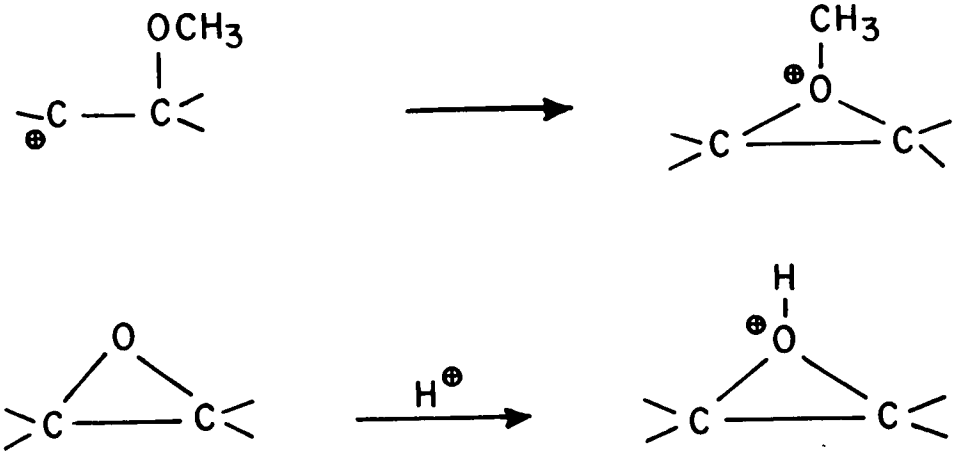


Figure 5. Potential S_N1 Mechanism for Oxygen-aglycone Bond Cleavage in 1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol

Alternatively, reaction of hydroxide ion with (X) could result in a mixture of 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol (IV) and 1,5-anhydro-2,3,6-tri-O-methyl-D-galactitol (VIII). The ratio of these two epimers would be determined by the approach preferred by the hydroxide ion. It is probable that shielding effects of the departing anion (IX) would cause the formation of (VIII) to dominate.

Brandon (4) found that oxygen-aglycone bond cleavage in (II) resulted in the formation of 1,5:3,6-dianhydro-D-galactitol from the aglycone, as well as unidentified products (fragments). The dianhydro-galactitol arises from intramolecular reactions of the S_N1cB type. Inversion of the pyranose ring to the C_4^1 conformation allows the conjugate base at C-3 to form 1,5:3,4-dianhydro-D-galactitol. Subsequent attack by the conjugate base at C-2 leads to a dianhydro-gulitol which undergoes reaction with the conjugate base of C-6 forming 1,5:3,6-dianhydro-D-galactitol. The proportion of dianhydro-galactitol formed from the intermediate C-4 carbonium ion is dependent on the reaction conditions. Stabilizing the carbonium ion by increasing the ionic strength of the medium from 0.5M to 2.5M results in the percentage of oxygen-aglycone bond cleavage proceeding via the carbonium ion rearrangement to form the unidentified products increasing from 26 to 54% (4). Therefore, since the completely methylated aglycone of (III) would tend to block the S_N1cB type rearrangements, it would be expected that an S_N1 mechanism for oxygen-aglycone bond cleavage would result in formation of the fragmentation products.

However, there is some evidence (16) that a trans methoxyl group can form a cyclic, three membered, methoxonium ion, which would behave similarly to an acid opening of the corresponding epoxide. In the case of (X) the resulting methoxonium ion would be in the 3,4-anhydro-D-galacto configuration.



In most cases, acid-catalyzed cleavage of 3,4-anhydro-D-galacto derivatives results in the formation of gulose sugars (17). In the rare instance in which some glucose derivatives arise from cleavage of the epoxide, it is as a mixture, with the gulose form dominating by a margin of 2:1 (18).

Consequently, in the unlikely event that formation of the cyclic methoxonium ion competes successfully with hydride transfer to form the resonance stabilized ion (XI), it is even less likely that significant quantities of (IV) would result.

KINETIC DESCRIPTION OF THE REACTION

DISAPPEARANCE OF THE REACTANT

1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol (0.01M) was reacted in oxygen-free aqueous sodium hydroxide (0.5-2.5N) for periods of 11-100 hours over the temperature range of 150-182°C. Equation (1) is the fundamental rate expression for the disappearance of the reactant:

$$d[R]/dt = -k\,[R]^{a} \int [OH^{-}] \qquad (1)$$

where k = specific rate constant,

$[R]$ = concentration of the reactant at time t, mole/liter,

$\int[OH^{-}]$ = an undetermined function of the hydroxide ion concentration,

and a = constant, initially assumed to be 1.0.

Since the concentration of sodium hydroxide was always maintained in large excess, from 50-250 times that of the reactant, its concentration remained essentially constant. Thus, the hydroxide ion function term in Eq. (1) would be constant, causing Eq. (1) to become:

$$d[R]/dt = -k_{r}[R] \qquad (2)$$

where k_{r} = the pseudo-first-order rate constant, sec^{-1}.

Integration of Eq. (2) yielded Eq. (3), which describes the disappearance of the reactant in this system.

$$\ln[R] = -k_{r}t + \ln[R]_{o} \qquad (3)$$

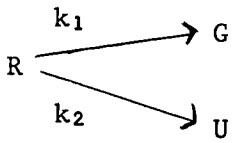
where $[R]_{o}$ = the initial concentration of the reactant.

The pseudo-first-order rate constants for reactant disappearance (k_r) were calculated in accordance with Eq. (3), evaluated by the method of least squares. Figure 6 is an example of data plotted according to Eq. (3). The linearity of the data confirms the assumption that the reaction is first order with respect to the reactant, i.e., a = 1.0.

APPEARANCE OF PRODUCTS

FORMATION OF 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-D-GLUCITOL

The kinetics of parallel first-order reactions, first-order reactions in which the reactant forms more than one product, are described in kinetics texts (19,20). For a reaction of the type:



the rate equation for the formation of an individual product is:

$$d[G]/dt = k_1[R]_o e^{-(k_1 + k_2)t} \qquad (4)$$

where [G] = the concentration of the product, in this case 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol, at time t.

Integration of Eq. (4) yields:

$$[G] = \{-k_1[R]_o/(k_1 + k_2)\}\ [e^{-(k_1 + k_2)t}] + C \qquad (5)$$

where C = the constant from the integration.

Setting $[G] = [G]_o$ at time t = 0 allows the constant (C) to be determined:

$$C = k_1[R]_o/(k_1 + k_2) + [G]_o$$

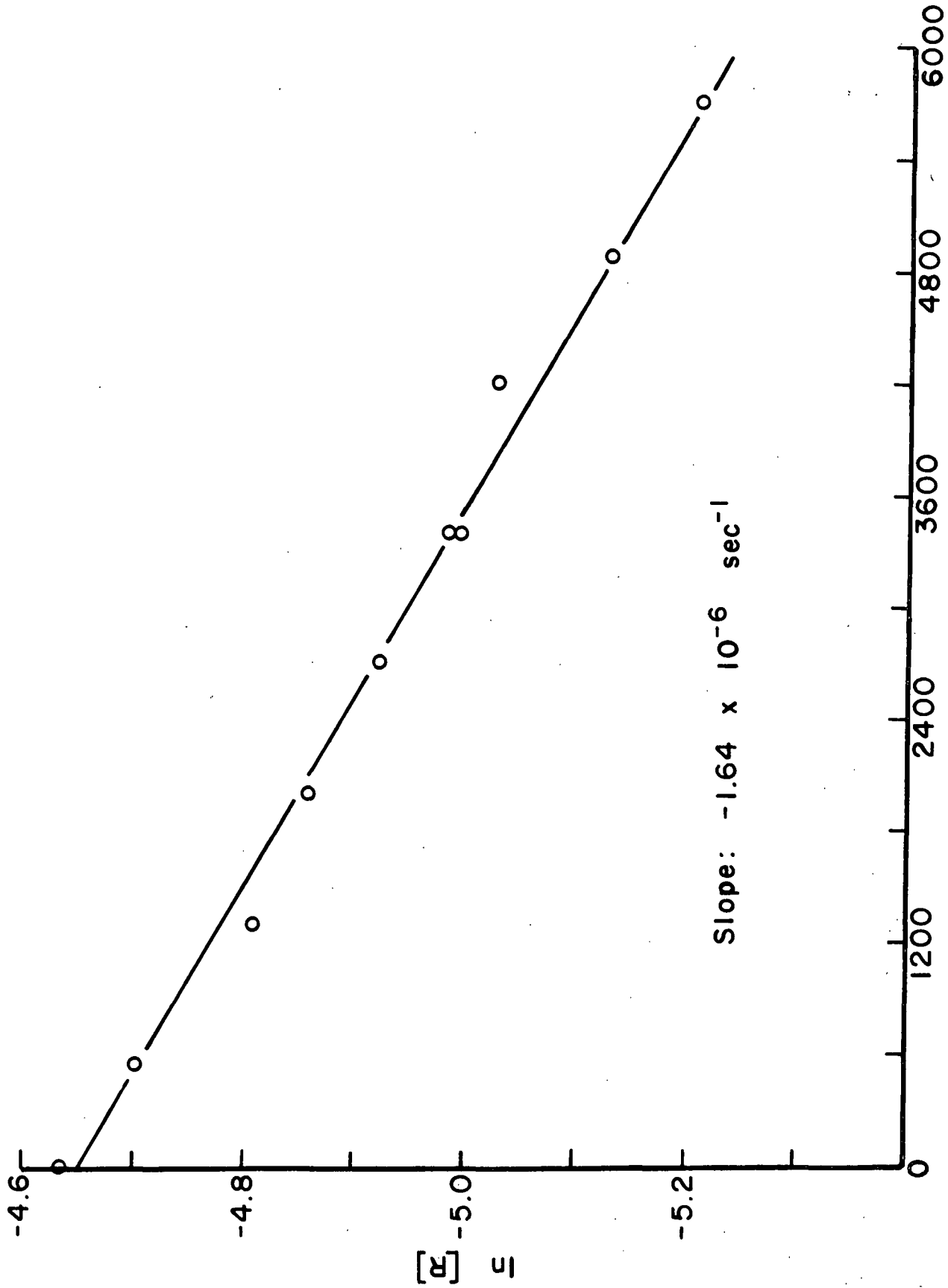


Figure 6. Determination of k_r for the Alkaline Degradation of 1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol in 2.5N NaOH at 151.4°C

where $[G]_o$ = the concentration of product at time t = 0*.

Since the total rate of reactant disappearance (k_r) is equal to the sum of the rates of formation of all the products ($k_1 + k_2$), substitution for C and ($k_1 + k_2$) in Eq. (5) yields:

$$[G] - [G]_o = (k_g[R]_o/k_r)\ (1 - e^{-k_r t}) \qquad (6)$$

where $k_g = k_1$ = the pseudo-first-order rate constant for the formation of 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol.

A typical plot of Eq. (6) is presented in Fig. 7. The slope of the line (k_g) was determined by the method of least squares.

FORMATION OF 1,6-ANHYDRO-β-D-GLUCOPYRANOSE

Determination of the rate of formation of 1,6-anhydro-β-D-glucopyranose (I) is not possible with Eq. (6), as (I) is not stable at the reaction conditions. This situation can be diagrammed as:

$$R \xrightarrow{k_{f1}} I \xrightarrow{k_{d1}} \text{acidic products}$$

where k_{f1} = the pseudo-first-order rate constant for the formation of 1,6-anhydro-β-D-glucopyranose

k_{d1} = the pseudo-first-order rate constant for the degradation of 1,6-anhydro-β-D-glucopyranose.

Therefore, the rate expression is:

$$d[L]/dt = k_{f1}[R] - k_{d1}[L] \qquad (8)$$

where [L] = the concentration of (I) at time t.

*Products could potentially be present at zero time, which was chosen as a short time (< 1% reaction) after the system had come to the desired temperature.

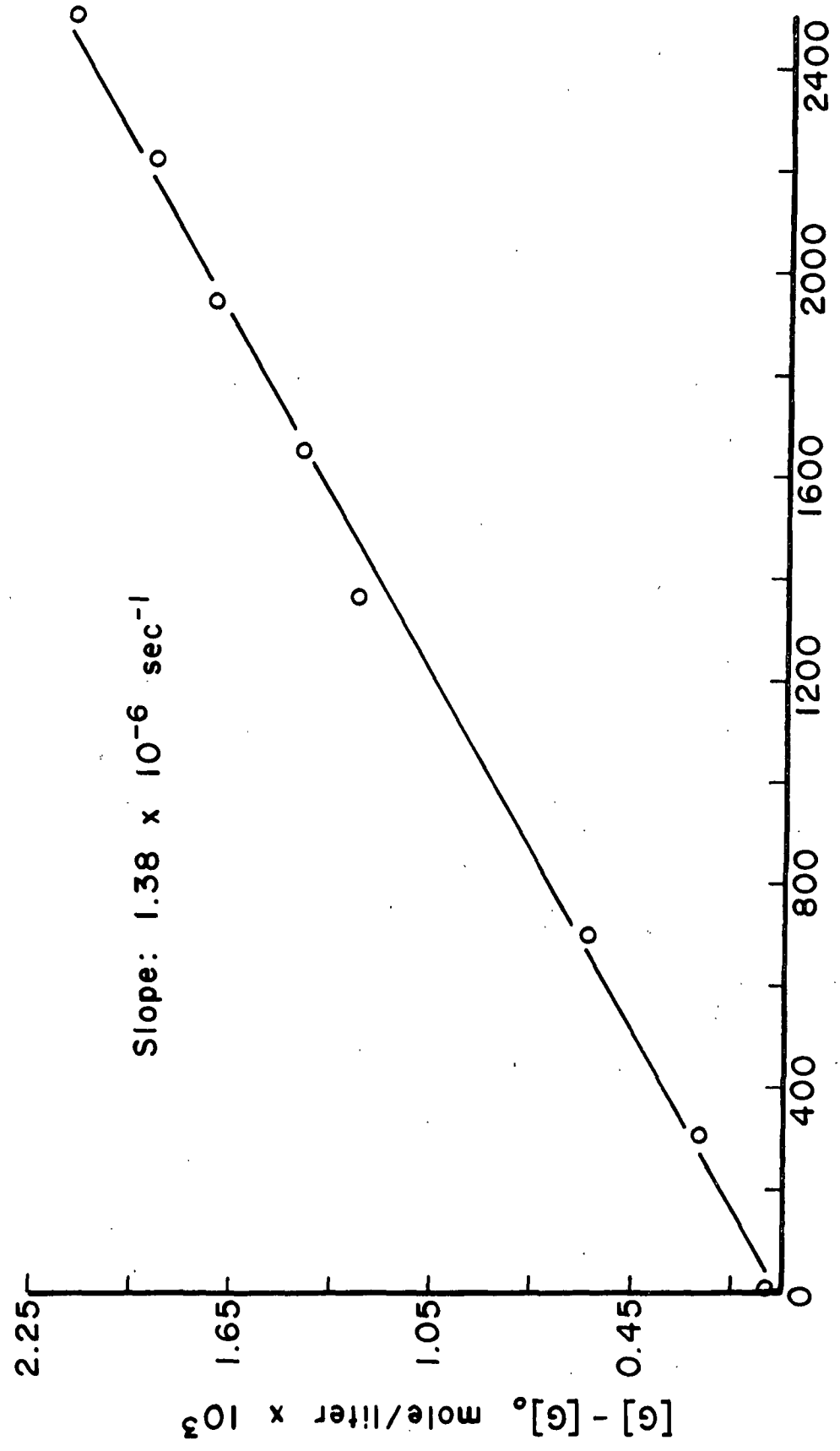


Figure 7. Determination of k_g for the Alkaline Degradation of 1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol in 2.5N NaOH at 151.4°C

Substituting ($[R]_o e^{-k_r t}$) for [R] Eq. (8) becomes:

$$d[L]/dt = k_{f1}[R]_o e^{-k_r t} - k_{d1}[L] \qquad (9)$$

Integration and rearrangement yields:

$$[L] = \{k_{f1}[R]_o e^{-k_r t}/(k_{d1}-k_r)\} + C\, e^{-k_{d1} t} \qquad (10)$$

where again C is the constant from the integration.

As was done with Eq. (5), setting $[L] = [L]_o$ at time t = 0 allows the constant C to be evaluated:

$$C = [L]_o - \{k_{f1}[R]_o(k_{d1} - k_r)\}$$

where $[L]_o$ is the initial concentration of 1,6-anhydro-β-D-glucopyranose (see footnote on page 22).

Equation (10) then becomes:

$$[L]-([L]_o e^{-k_{d1} t}) = \{k_{f1}[R]_o/(k_{d1}-k_r)\}\ \{(e^{-k_r t})-(e^{-k_{d1} t})\} \qquad (11)$$

Values for the pseudo-first-order rate constant for the degradation of 1,6-anhydro-β-D-glucopyranose (k_{d1}) at the conditions employed during this study were independently determined by Gilbert (5). Figure 8 is a representative plot of Eq. (11), with the slope being calculated by the method of least squares.

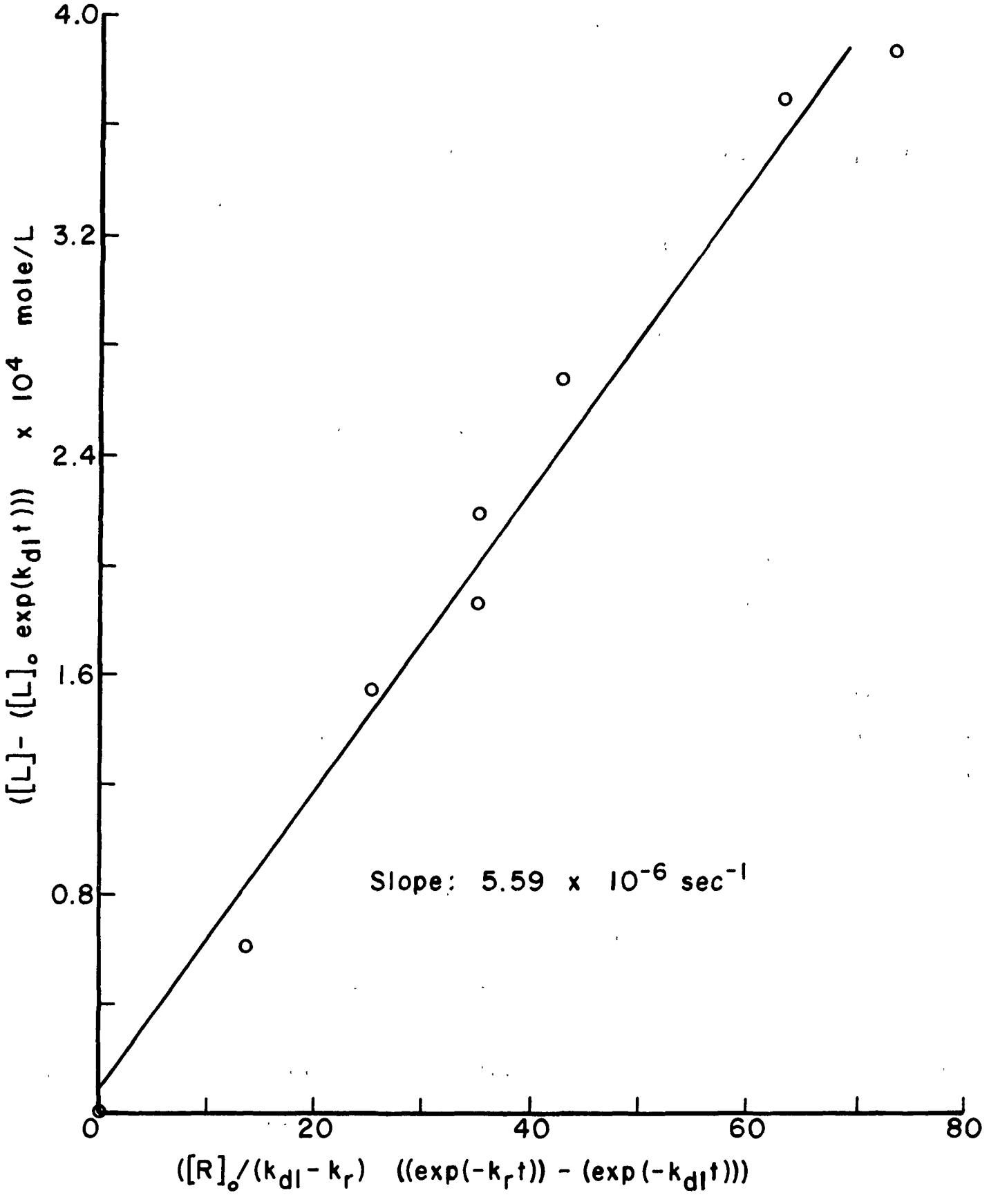


Figure 8. Determination of k_{fl} for the Alkaline Degradation of 1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol in 2.5N NaOH at 171.2°C

RESULTS AND DISCUSSION

PRODUCT DISTRIBUTION

As expected, the major stable product of the alkaline degradation of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol (III) was 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol (IV). This compound could be taken as a measure of glucosyl-oxygen bond cleavage provided that oxygen-aglycone bond cleavage did not also produce significant amounts of (IV). The potential mechanisms for oxygen-aglycone bond cleavage indicate that production of 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol (IV) should be accompanied by equal or greater formation of 1,5-anhydro-2,3,6-tri-O-methyl-D-galactitol (VIII). To ensure that the analytical techniques could distinguish between the two epimers, the galactitol derivative (VIII) was synthesized and subjected to the same work-up procedure as the kinetic samples. The gas chromatographic conditions employed in this study adequately resolved the epimers, as illustrated by the sample chromatogram presented in Fig. 9. During the course of the studies only trace quantities of the galactitol (VIII) [< 0.5% based on the glucitol (IV)] were encountered. Therefore, the pseudo-first-order rate constant for the formation of 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol (IV) was taken as the measure of glucosyl-oxygen bond cleavage in the disaccharides studied.

It was previously shown that 1,5-anhydro-D-glucitol was stable in alkaline solutions at these temperatures (14). It was initially assumed that the methylated derivative (IV) would likewise be stable in alkali. However, this was checked experimentally. 1,5-Anhydro-2,3,6-tri-O-methyl-D-glucitol (IV) was subjected to 2.5N NaOH at 170°C with the result that 97.5% of the starting material remained after 273 hours (17 half-lives of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol).

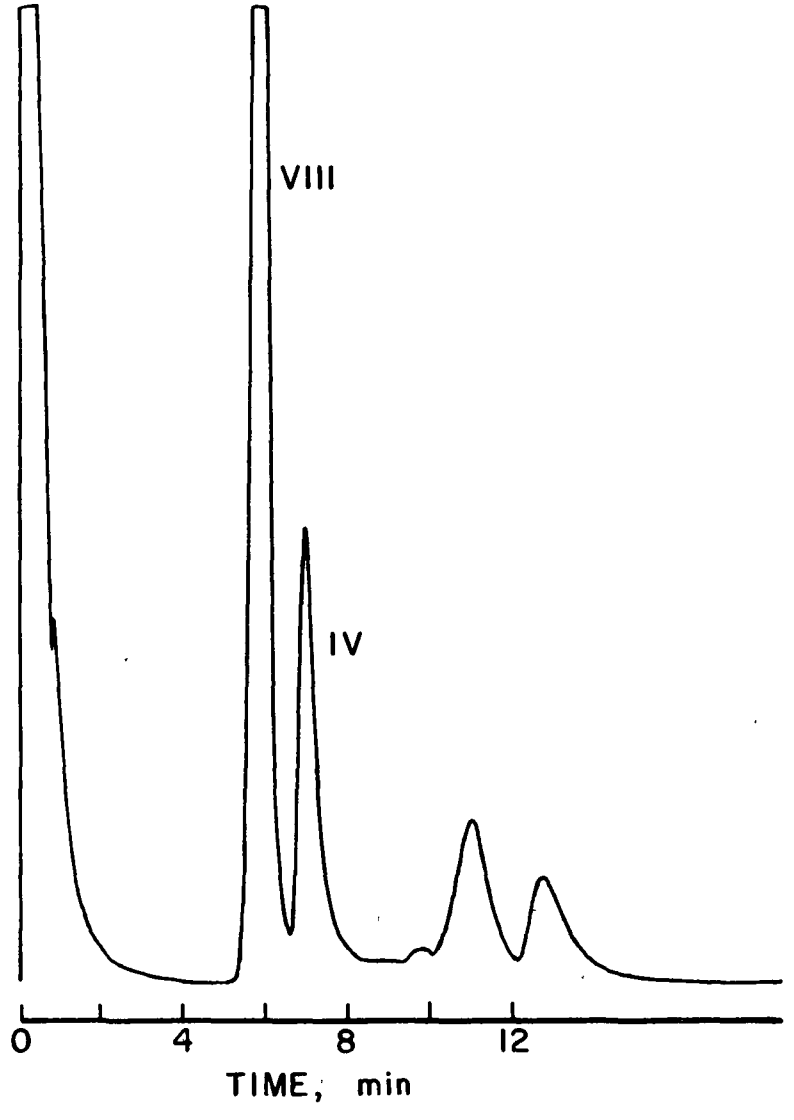


Figure 9. The Gas Chromatographic Resolution of 1,5-Anhydro-2,3,6-tri-O-methyl-D-glucitol (IV) and 1,5-Anhydro-2,3,6-tri-O-methyl-D-galactitol (VIII)

The other identified product was 1,6-anhydro-β-D-glucopyranose (I), which was only partially stable at the reaction conditions. It was present in relatively low concentrations due to the fact that the pseudo-first-order rate constant for the degradation of (I) (k_{d1}) was considerably larger than the pseudo-first-order rate constant for its formation (k_{f1}).

Depending upon the conditions, a difference (up to 20%) was observed between the moles of (III) reacted and the moles of (IV) formed from the aglycone. The deficit is believed to be the result of the formation of acidic products, or small fragments, which were not resolved by the techniques employed. The same applies to the difference between the moles of (III) reacted and the quantities of (I) formed from the glucosyl moiety.

GLUCOSYL-OXYGEN BOND CLEAVAGE

APPARENT THERMODYNAMIC FUNCTIONS OF ACTIVATION

The pseudo-first-order rate constants for the degradation of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol in 2.5N sodium hydroxide were determined over the temperature range of 151-182°C. The results of these experiments are presented in Table II. Analysis of these data allowed the apparent thermodynamic functions of activation to be calculated (see Appendix I). Due to the fact that the calculations were based on pseudo-first-order rate constants, not the true specific rate constants, the resultant values are termed apparent.

Mechanisms are based on numerous factors, all of which are consistent with the postulated mechanism, but taken individually may not confirm a mechanism. Thus, any conclusions drawn from the apparent thermodynamic functions of activation must be done judiciously. Mechanistic implications can be drawn by comparing these values to those of related compounds, whose mechanisms are presumed to be known. The apparent thermodynamic functions of activation have been determined for the alkaline degradation of several alkyl glycosides and disaccharides (4,5) under conditions similar to those used in this study. Table III is a comparison of the apparent thermodynamic functions for selected saccharides representative of the

potential mechanisms for glucosyl-oxygen bond cleavage of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol.

TABLE II

THE EFFECT OF TEMPERATURE ON THE DEGRADATION OF 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL (0.01M) IN 2.5N NaOH

Temp., °C	k_r [a] x 10^6 sec^{-1}	k_g [b] x 10^6 sec^{-1}	k_1 [c] x 10^6 sec^{-1}	X_g [d]	X_1 [e]
151.4	1.66	1.38	1.05	0.831	0.761
161.9	4.65	4.10	2.72	0.882	0.663
171.2	12.1	11.6	5.59	0.959	0.482
171.4	11.8	10.9	6.43	0.924	0.590
182.1	26.4	24.4	12.6	0.924	0.516

[a] Pseudo-first-order rate constant for the disappearance of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol.
[b] Pseudo-first-order rate constant for the formation of 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol.
[c] Pseudo-first-order rate constant for the formation of 1,6-anhydro-β-D-glucopyranose.
[d] Mole fraction of 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol formed, defined as k_g/k_r.
[e] Mole fraction of 1,6-anhydro-β-D-glucopyranose formed, based on cleavage of the glucosyl-oxygen bond, defined as k_1/k_g.

As would be anticipated, the highest value for $\Delta H^{\ddagger}$ in the reference compounds belongs to the S_N1 mechanism. The enthalpy of activation is a measure of the energy needed to promote bond cleavage as the reactant(s) move to the activated complex of the transition state. The rate determining step in an S_N1 reaction is the formation of a carbonium ion, which subsequently forms a new bond with an available nucleophile. Thus, none of the energy released by bond formation is available to reduce the energy for the initial bond cleavage. In the transition state of both the S_N2 and $S_NlcB(2)$ mechanisms bond cleavage occurs concurrently with bond formation, which lowers the activation energy. Thus, it would be expected that

the enthalpies of activation for the S_N2 and $S_N1cB(2)$ mechanisms would be similar to each other, while both would be lower than for an S_N1 mechanism.

TABLE III

COMPARISON OF APPARENT THERMODYNAMIC FUNCTIONS OF ACTIVATION FOR ALKALINE DEGRADATIONS IN 2.5N NaOH AT 170°C

Compound	Proposed Mechanism	E_a, kcal/mole	$\Delta H^{\ddagger}$, kcal/mole	$\Delta S^{\ddagger}$, e.u.
1,5-Anhydrocellobiitol, oxygen-aglycone bond (4)	S_N1	42.6	41.7	+6.9
Methyl α-D-glucopyranoside (5)	S_N2	32.0	31.1	-17.5
1,6-Anhydro-β-D-glucopyranose (5)	$S_N1cB(2)$	33.7	32.8	-3.8
1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol, glucosyl-oxygen bond[a]	--	36.4	35.5	-3.2

[a] Calculation based on the pseudo-first-order rate constant for formation of 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol (k_g).

The enthalpy of activation for glucosyl-oxygen bond cleavage of (III) is considerably lower than the reference value for an S_N1 mechanism. However, it is also a little higher than the value for 1,6-anhydro-β-D-glucopyranose. This would be expected for the 1,6-anhydride (I) is locked in the higher energy C_4^1 conformation, while the glucosyl moiety of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol would favor the lower energy C_1^4 conformation. Additional energy would be required to invert the conformation of the pyranose ring to the C_4^1 conformer to achieve the trans-1,2 diaxial orientation necessary for the $S_N1cB(2')$ mechanism to function. Should an S_N2 mechanism govern glucosyl-oxygen bond cleavage in (III), $\Delta H^{\ddagger}$ would be expected to be close to the reference value, for like the S_N1 reaction, no additional energy would be required.

The entropy of activation is indicative of variations in the total degrees of freedom between the reactants and the transition state. Since this quantity also measures structural changes of the solvent as well, absolute values for the entropy changes cannot be made. Fortunately, the transition states of the potential mechanisms are different enough to allow for prediction of significant entropy changes among them, provided the media changes are essentially the same. In an S_N1 reaction two species are formed from the single reactant molecule, an entropy-favored process. The $S_N1cB(2')$ mechanism is entirely a unimolecular process in the transition state, as the cleaving of the glucosyl-oxygen bond occurs simultaneously with the forming of the 1,2-anhydride. This type of reaction should exhibit an entropy of activation less than that for a comparable S_N1 reaction. In the instance of an S_N2 reaction, the formation of a single complex species from two previously independent molecules occurs in the transition state. Its entropy of activation would be more negative than either of the other potential mechanisms. As seen in Table III, the value of $\Delta S^{\ddagger}$ for glucosyl-oxygen bond cleavage is in good agreement with what would be expected for an $S_N1cB(2')$ mechanism.

Therefore, based on the apparent thermodynamic functions of activation, it is indicated that the glucosyl-oxygen bond of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol cleaves via an $S_N1cB(2')$ mechanism.

EFFECT OF IONIC STRENGTH AT CONSTANT HYDROXIDE CONCENTRATION

Increasing the dielectric constant of the solvent, or increasing the concentration of ions, would stabilize the ionic species present during the course of the reaction. Thus, the salt effect would accelerate the rate of an S_N1 reaction, since the transition state, which is composed of two charged species, would be more stabilized than the neutral reactant. In the case of the other two potential mechanisms the reverse would be true. The reactants are charged, leading to increased stabilization in the ground state, and hence a lower rate of reaction.

In this study the effect of ionic strength of the medium was investigated by addition of weakly nucleophilic sodium p-toluene sulfonate to 0.5N NaOH. As the data in Table IV show, increasing the ionic strength from 0.5-2.5M, at a constant concentration of hydroxide ion (0.5N), resulted in a 19.5% decrease in the pseudo-first-order rate constant for cleavage of the glucosyl-oxygen bond of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol (k_g).

TABLE IV

THE EFFECT OF IONIC STRENGTH AT CONSTANT HYDROXIDE ION CONCENTRATION (0.5N) ON GLUCOSYL-OXYGEN BOND CLEAVAGE IN 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL (0.01M) AT 170°C

Ionic Strength, M	x 10^6 sec^{-1}				
	k_r [a]	k_g [b]	k_1 [c]	X_g [d]	X_1 [e]
0.5	4.30	3.43	2.30	0.798	0.671
2.5	3.30	2.76	2.32	0.836	0.841

[a] Pseudo-first-order rate constant for the disappearance of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol.
[b] Pseudo-first-order rate constant for the formation of 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol.
[c] Pseudo-first-order rate constant for the formation of 1,6-anhydro-β-D-glucopyranose.
[d] Mole fraction of 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol formed, defined as k_g/k_r.
[e] Mole fraction of 1,6-anhydro-β-D-glucopyranose formed, based on cleavage of the glucosyl-oxygen bond, defined as k_1/k_g.

The magnitude, and direction, of the observed salt effect compares well with the 19.3% decrease in the pseudo-first-order rate constant for the degradation of 1,6-anhydro-β-D-glucopyranose under similar conditions, which was concluded to degrade via an $S_N1cB(2)$ mechanism. Reference values for the other potential mechanisms are: methyl α-D-glucopyranoside (S_N2), -25.2% (5) and the oxygen-aglycone bond of 1,5-anhydrocellobiitol (S_N1), +64% (14).

While the ionic strength data is consistent with an $S_N1cB(2')$ mechanism, salt effects for other organic solvent reactions are generally higher. There are two reasons why a lower value would be expected in this system. In the $S_N1cB(2')$ mechanism the first step is the reversible ionization of the appropriate hydroxyl group, as depicted by Eq. (12). This is followed

$$ROH \underset{}{\overset{K_e}{\rightleftharpoons}} RO^- \xrightarrow{k} \text{Products} \qquad (12)$$

by the rate determining step resulting in the formation of the products. Therefore, while increasing the ionic strength slows the formation of products by stabilization of the charged species (RO^-), it also forces the ionization equilibrium to the right, which results in a higher concentration of RO^-. Thus, the net salt effect, measured by the rate of product formation, is lower than what would be expected for a single step reaction. Also, increasing the dielectric constant of the solvent can produce the same result as addition of an ionic species. Since the solvent in this system is water, which has a very high dielectric constant, it could exhibit a "leveling effect" (4), which would cause the increased levels of ions to have less of an effect than they would in a less polar solvent.

Unfortunately, no data on the activity of sodium hydroxide in aqueous solutions at temperatures above 70°C. are available. Thus, accurate discussion concerning changes in the activity of hydroxide ion when the total ionic strength is increased from 0.5M to 2.5M is not possible at present. If the temperature dependence, determined from data gathered up to 70°C, can be extrapolated to 170°C, the value of the activity coefficient for a 0.4 molal solution of NaOH is 0.56, while 3 molal NaOH has an activity coefficient of 0.49 (21). What the effect of increasing the total ionic strength from 0.5M to 2.5M with sodium p-toluene sulfonate, instead of additional hydroxide, is not known.

However, the mechanistic implications are the same be it a true salt effect, or a combination of that and a change in the activity of hydroxide ion. Increasing the total ionic strength of 0.5M NaOH to 2.5M by addition of sodium p-toluenesulfonate causes the pseudo-first-order rate constant for an S_N1 reaction to increase (4), while the rate of an $S_N1cB(2)$, or S_N2, reaction decreases (5).

In the next section a similar situation concerning the activity of sodium hydroxide exists. The true activity of the NaOH is not known at the various concentrations employed, but the total ionic strength of the medium is maintained at a constant level so as to minimize any activity changes.

EFFECT OF VARYING THE HYDROXIDE ION CONCENTRATION AT CONSTANT IONIC STRENGTH

Based on the data presented thus far, it appears that the mechanism governing glucosyl-oxygen bond cleavage in 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol is the $S_N1cB(2')$ pathway. Lai (13) has proposed a linear reciprocal relationship for reactions of the type described by Eq. (12). The rate of the alkaline degradation is expressed in Eq. (13):

$$d[P]/dt = k[RO^-] \qquad (13)$$

where $[P]$ = the concentration of products formed at time t

and $[RO^-]$ = the concentration of the intermediate oxyanion at t.

From Eq. (12) the equilibrium constant for the ionization can be expressed as:

$$K_e = [RO^-]/\{[ROH]_o - [RO^-] - [P]\}\ OH^- \qquad (14)$$

where $[ROH]_o$ = the initial concentration of reactant.

Combining Eq. (13) and (14) and integrating yields:

$$\ln \frac{[ROH]_o - [P]}{[ROH]_o} = - \frac{K_e k[OH^-]}{1 + K_e[OH^-]} \; t \qquad (15)$$

Equation (15) is similar in form to the one governing reactant disappearance in this system [Eq. (3)]. Therefore, the pseudo-first-order rate constant observed (k_{obs}) can be related to Eq. (15) by Eq. (16).

$$k_{obs} = \frac{K_e k[OH^-]}{1 + K_e[OH^-]} \qquad (16)$$

Inversion of Eq. (16) yields the reciprocal relationship.

$$1/k_{obs} = 1/k + 1/kK_e[OH^-] \qquad (17)$$

One assumption that is made is that sodium hydroxide is completely dissociated at the reaction conditions. This assumption was made in previous work (2-5, 13), and is carried over in this study. Consequently, the concentration of hydroxide ion was taken as the concentration of sodium hydroxide.

To test the applicability of this theory to the degradation of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol, four reactions were conducted at varying hydroxide ion concentrations, while the total ionic strength was maintained at a constant level. The total ionic strength must be maintained in order to avoid changes in the activity coefficient of the hydroxide ion (14). The data are presented in Table V. The rate constants for glucosyl-oxygen bond cleavage (k_g) were adjusted to a constant temperature (170°C) with Eq. (18) (5) and plotted according to Eq. (17). The expected linearity of the plot is seen in Fig. 10.

$$\ln k_1 = \ln k_2 - E_a/R(1/T_1 - 1/T_2)^{*,**} \qquad (18)$$

---

*The assumption is made that the activation energy is independent of the hydroxide **ion concentration. This was found to be the case in similar studies (2,5,14).
The temperatures are °K.

where k_1 = the rate constant at temperature T_1,

k_2 = the rate constant at temperature T_2

R = the universal gas constant (1.987 cal/mole-°K)

and E_a = the Arrhenius activation energy.

TABLE V

EFFECT OF HYDROXIDE ION CONCENTRATION ON THE DEGRADATION OF 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL AT THE CONSTANT IONIC STRENGTH OF 2.5M

Temp., C	OH^-, N	x 10^6 sec^{-1}				
		k_r [a]	k_g [b]	k_1 [c]	X_g [d]	X_1 [e]
171.3[f]	2.50	11.95	11.25	6.01	0.941	0.534
170.8	1.50	5.99	5.80	3.53	0.968	0.609
171.2	0.75	4.47	3.83	2.95	0.857	0.770
171.6	0.50	3.30	2.76	2.32	0.836	0.841

[a] Pseudo-first-order rate constant for the disappearance of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol.

[b] Pseudo-first-order rate constant for the formation of 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol.

[c] Pseudo-first-order rate constant for the formation of 1,6-anhydro-β-D-glucopyranose.

[d] Mole fraction of 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol formed, defined as k_g/k_r.

[e] Mole fraction of 1,6-anhydro-β-D-glucopyranose formed, based on cleavage of the glucosyl-oxygen bond, defined as k_1/k_g.

[f] Average of duplicate determinations.

While this treatment of the hydroxide data is consistent with an $S_N1cB(2')$ mechanism, reciprocal relationships of this nature were also found for other systems in which ionization of hydroxyl groups was possible. For example, the hydroxide ion data for the degradation of methyl α-D-glucopyranoside, which was shown to degrade via an S_N2 mechanism, also yielded a linear plot for $1/[OH^-]$ vs. $1/k_{obs}$ (5).

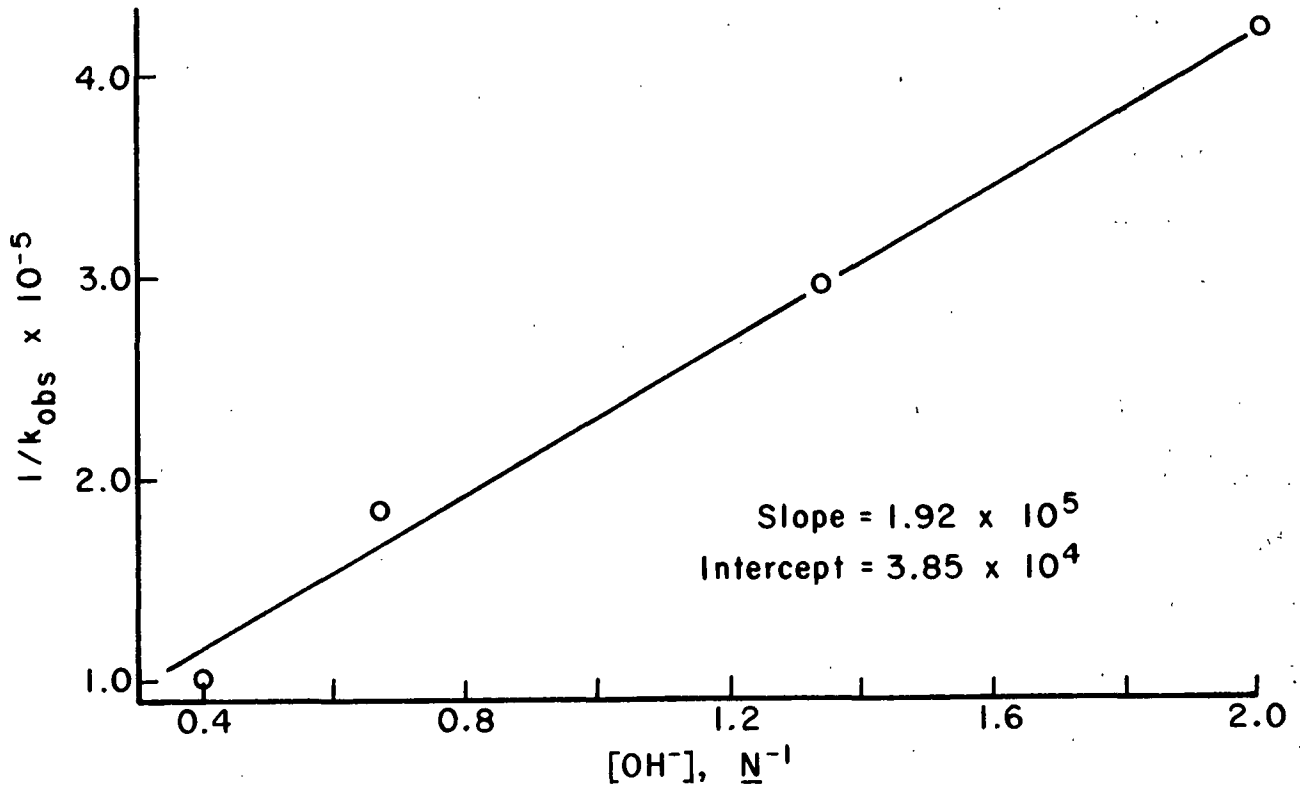


Figure 10. The Dependence of the Pseudo-first-order Rate Constant on the Hydroxide Ion Concentration

However, the mechanistic implications from such linear relationships lie in the interpretations of the slope and the intercept. This is illustrated in the expanded kinetic treatment of the hydroxide ion data for 1,6-anhydro-β-D-glucopyranose and methyl α-D-glucopyranoside (5). If, as the data indicates, glucosyl-oxygen bond cleavage in 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol is governed by the $S_N1cB(2')$ mechanism, the intercept from Fig. 10 should be the inverse of the specific rate constant for displacement of the aglycone by the C-2' oxyanion. Also, the ratio of intercept: slope is K_e, the equilibrium constant for the ionization of the C-2' hydroxyl group.

From Fig. 10 the value for K_e is 0.20. This compares well with 0.21, found for methyl α-D-glucopyranoside (5), but differs from the value of 0.47 determined

for 1,6-anhydro-β-D-glucopyranose (5). The difference is not unexpected, for the 1,6-anhydride is locked in the C_4^1 conformation, keeping the C-2 hydroxyl in an axial position. This should result in a higher K_e, for it has been indicated that axial hydroxyls are more acidic than their equatorial epimers (22).

EFFECT OF BLOCKING THE IONIZATION OF THE C-2' HYDROXYL GROUP

If an $S_N1cB(2')$ mechanism is governing the cleavage of the glucosyl-oxygen bond in 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol, initial formation of the conjugate base at C-2' is required. By methylating the C-2' hydroxyl group ionization is prevented, which should result in a marked decrease in the pseudo-first-order rate constant for glucosyl-oxygen bond cleavage for the methylated derivative. This approach has been employed by Gasman and Johnson (23) and Gilbert (5) to support proposed $S_N1cB(2)$ mechanisms for the alkaline degradations of p-nitrophenyl β-D-galactopyranoside and p-nitrophenyl α-D-mannopyranoside, and 1,6-anhydro-β-D-glucopyranose, respectively. The second order rate constant* for the p-nitrophenyl glycosides decreased by more than 99%, while the pseudo-first-order rate constant for 1,6-anhydro-β-D-glucopyranose decreased by more than 96%, upon methylation of their respective C-2 hydroxyl groups (Table VI).

To determine the effect of a 2'-O-methyl substituent on the alkaline degradation of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol, kinetic experiments were conducted with 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol and 1,5-anhydro-2,3,6,2',3'-penta-O-methyl-cellobiitol [1,5-anhydro-4-O-(2,3-di-O-methyl-β-D-glucopyranosyl)-2,3,6-tri-O-methyl-D-glucitol] under indentical conditions. The results, which are presented in Table VII, show that a 2'-O-methyl substituent causes more than a

*In contrast to the current work, the concentration of sodium hydroxide was not maintained in large excess. Hence, the rate constants cannot be termed pseudo-first-order, as the concentration of hydroxide ion changed over the course of the reaction.

97% reduction in the pseudo-first-order rate constant for glucosyl-oxygen bond cleavage (k_g). This confirms the importance of the ionization of the C-2' hydroxyl group, and is consistent with an $S_N1cB(2')$ mechanism.

TABLE VI

RATE CONSTANTS FOR SELECTED GLYCOSIDES AND THEIR 2-O-METHYL DERIVATIVES IN ALKALINE MEDIA

Compound	k x 10^6 sec^{-1}
p-Nitrophenyl β-D-galactopyranoside	416.0[a]
p-Nitrophenyl 2-O-methyl-β-D-galactopyranoside	1.26[a]
p-Nitrophenyl α-D-mannopyranoside	3090.0[a]
p-Nitrophenyl 2-O-methyl-α-D-mannopyranoside	1.65[a]
1,6-Anhydro-β-D-glucopyranose	52.4[b]
1,6-Anhydro-2-O-methyl-β-D-glucopyranose	1.90[b]

[a] Measured at 55°C.
[b] Measured at 170°C.

TABLE VII

PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE ALKALINE DEGRADATION OF 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL AND 1,5-ANHYDRO-2,3,6,2',3'-PENTA-O-METHYL-CELLOBIITOL AT 171°C and 2.5N NaOH

Compound	x 10^6 sec^{-1}		
	k_r[a]	k_g[b]	k_{r-g}[c]
1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol[d]	11.95	11.25	0.70
1,5-Anhydro-2,3,6,2',3'-penta-O-methyl-cellobiitol	0.995	0.322	0.673

[a] Pseudo-first-order rate constant for disappearance of the reactant.
[b] Pseudo-first-order rate constant for the formation of 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol.
[c] Pseudo-first-order rate constant for oxygen-aglycone bond cleavage, $k_r - k_g$.
[d] Average of duplicate determinations.

The slight reactivity of 1,5-anhydro-2,3,6,2',3'-penta-O-methyl-cellobiitol's glucosyl-oxygen bond (cleavage of the oxygen-aglycone bond should be unaffected, as Table VII indicates) may be due to a mechanism that is also operative in the glucosyl-oxygen cleavage of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol. However, the value of elucidating this mechanism would be of minimal importance, for the total amount of the overall reactivity for which it is responsible is quite small. Furthermore, it would be difficult to distinguish if the particular mechanism was normally operative in the glucosyl-oxygen cleavage of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol, or only becomes active when the favored $S_N1cB(2')$ pathway is blocked.

Studies of molecular models of 1,6-anhydro-2-O-methyl-β-D-glucopyranose indicated that rotation of the methyl group about its ether linkage might interfere with the approach of hydroxide ion, thus causing a decrease in the reaction rate relative to the unmethylated derivative (5). However, such steric hindrance would be unlikely to cause such a large decrease in the reaction rate. Also, besides the positive evidence for the $S_N1cB(2')$ mechanism already discussed, the large quantities of 1,6-anhydro-β-D-glucopyranose formed from glucosyl-oxygen bond cleavage in 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol indicate that an S_N2 mechanism is not likely.

OXYGEN-AGLYCONE BOND CLEAVAGE

NEIGHBORING GROUP MECHANISMS

1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol has no ionizable hydroxyl groups on the aglycone. Therefore, the operation of a neighboring group mechanism in oxygen-aglycone bond cleavage is not possible.

S_N2 MECHANISM

Due to inversion of configuration at the reactive site, if the oxygen-aglycone bond of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol cleaved via an S_N2 mechanism, the sole product from the aglycone would be 1,5-anhydro-2,3,6-tri-O-methyl-D-galactitol. Since no significant quantities of this compound were found during the course of this study, the S_N2 pathway can be ruled out as a potential mechanism for oxygen-aglycone cleavage.

S_N1 MECHANISM

Data from the oxygen-aglycone bond cleavage of 1,5-anhydro-cellobiitol led to the conclusion that it cleaved via the S_N1 mechanism. 1,5:3,6-Dianhydro-D-galactitol was found to be the only stable product formed from oxygen-aglycone cleavage. Thus, the thermodynamic functions of activation for its production were representative of the oxygen-aglycone bond as a whole (14). The values found for $\Delta H^{\ddagger}$, 42.1 kcal/mole, and $\Delta S^{\ddagger}$, +7 e.u., compared favorably with the values found for sodium methyl α-D-glucopyranosiduronate ($\Delta H^{\ddagger}$ 40.0 kcal/mole, $\Delta S^{\ddagger}$ +15 e.u.) (2), which was concluded to degrade via an S_N1 mechanism. Also, a salt effect of +64% and a slight negative dependence on increasing hydroxide ion concentration were consistent with the S_N1 mechanism.

The reproducibility of the kinetic data, determined by duplicate determinations of the degradation of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol in 2.5N NaOH at 171°C (Table II), was $\pm 0.15 \times 10^{-6}$ sec.$^{-1}$ (±1.3%) for the disappearance of the reactant (k_r) and $\pm 0.35 \times 10^{-6}$ sec.$^{-1}$ (±3.1%) for the formation of 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol (k_g). Since no stable products from the aglycone were detected, cleavage of the oxygen-aglycone bond was measured by the difference in the overall reaction rate (k_r) and the cleavage of the glucosyl-oxygen bond (k_g). This resulted in a reproducibility of $\pm 0.2 \times 10^{-6}$ sec.$^{-1}$

which, due to the low cleavage rate in relation to the glucosyl-oxygen bond, was ±28.6%. Therefore, accurate determinations of the thermodynamic functions of activation, and media change dependencies, were not possible.

In the degradation of 1,5-anhydrocellobiitol the standard deviation for triplicate determinations of oxygen-aglycone cleavage by the method of subtracting the rate of glucosyl-oxygen cleavage from the rate of reactant disappearance was $\pm 0.23 \times 10^{-6}$ sec.$^{-1}$ (±39%) (4,14). Therefore, the data presented in Table VIII is in general agreement, considering the variation encountered when working with the difference of two experimentally determined values of low magnitude.

TABLE VIII

COMPARISON OF THE RATES OF OXYGEN-AGLYCONE BOND CLEAVAGE IN 1,5-ANHYDRO-CELLOBIITOL AND 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL

Temp., C	NaOH, M	Ionic Strength, M	x 10^6 sec^{-1} k_{ac} [a]	k_{tmc} [b]	$k_{tmc} - k_{ac}$
170	0.5	2.5	0.87	0.54	-0.33
170	1.0	2.5	0.84	0.19	-0.65
170	2.5	2.5	0.59	0.70	+0.11
170	0.5	0.5	0.53	0.87	+0.34
160	2.5	2.5	0.37	0.55	+0.18
180	2.5	2.5	2.36	2.00	-0.35
				Average Difference	-0.12

[a] Oxygen-aglycone cleavage in 1,5-anhydro-cellobiitol determined by the difference in the rate of reactant disappearance and the rate of glucosyl-oxygen bond cleavage.

[b] Oxygen-aglycone cleavage in 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol determined by the difference in the rate of reactant disappearance and the rate of glucosyl-oxygen bond cleavage.

In view of the fact that the rate of oxygen-aglycone bond cleavage in 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol is on the order of that found for 1,5-anhydrocellobiitol, which was concluded to react via the S_N1 mechanism, and there is no evidence supporting the other potential mechanisms, it is concluded that the oxygen-aglycone bond of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol also cleaves via the S_N1 mechanism.

CONCLUSIONS

From the experimental data obtained in this investigation, along with theoretical considerations and comparisons with previously reported results, an $S_N1cB(2')$ mechanism (Fig. 1) is proposed for the oxygen-free alkaline degradation of the glucosyl-oxygen bond of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol. Cleavage of the oxygen-aglycone bond is proposed to occur via an S_N1 mechanism (Fig. 5).

EXPERIMENTAL

GENERAL

The reaction system used to conduct the kinetic studies in this investigation was originally constructed by Brandon (4), and subsequently modified by Gilbert (5).

Melting points were determined with a Thomas Hoover Capillary apparatus which had been calibrated against known compounds.

Optical rotations were measured on a Perkin-Elmer 141 MC recording polarimeter.

Elemental analyses were performed by Chemalytics, Inc. (2330 South Industrial Park Drive, Tempe, Arizona).

Nuclear magnetic resonance spectra were determined on a JEOL FX-100 Fourier transform NMR spectrometer using tetramethylsilane as the internal standard in the appropriate deuterated solvent. All spectra were obtained at the normal probe temperature.

Thin-layer chromatography was performed using glass microscope slides coated with Silica Gel G (Brinkman Instruments). The developing solutions are indicated in the appropriate sections. Spot visualization was accomplished by spraying with 20% (wt.) sulfuric acid in methanol, followed by charring.

Gas-liquid chromatography was conducted on a Varian Aerograph 1200-1 instrument, equipped with a flame ionization detector, and a Honeywell Electronic 16 recorder equipped with a Disc Integrator. Prepurified nitrogen (Matheson Gas Products) was used as the carrier gas. Operating conditions, retention times, and response factors are given in Appendix II.

Mass spectra were obtained with a Dupont Instruments Model 21-491 mass spectrometer interfaced with a varian Aerograph Model 1440-1 gas chromatograph. A Hewlett-Packard Model 7128A recorder was used to record the gas chromatograms, while the mass spectra were recorded on a Century GPO 460 recorder. The m/e values were assigned by running the compound alone and comparing its spectrum to one in which a small amount of internal standard (perfluorokerosene, low mass) had been added to the sample.

PROCEDURES FOR KINETIC ANALYSES

The preparation of reaction solutions and the loading of the reactor has been previously described (4,5). All calculations of concentrations were based on the reaction temperature, which necessitates incorporating the volume expansivity factor for the solution, as described by Gilbert (5).

The weight of each sample (ca. 1 g) was determined and the internal standard solutions (n-propyl β-D-xylopyranoside for the monosaccharides and cyclohexyl β-cellobioside for the disaccharides) were added gravimetrically. The samples were deionized, removing salts and acidic compounds, by passing them through a column (10 mm, ID) containing MB-3 (H^+, OH^-) resin (10-15 mL) and eluting with water (20 mL). The samples were run through the same resin again and eluted with water (10 mL) if the pH of the original elutant was outside the 5-7 range. The samples were concentrated to dryness in vacuo using a bath temperature of less than 45°C. The samples were dissolved in pyridine (1 mL) and acetic anhydride (1 mL) and shaken mechanically for 18 hours. The acetylation was quenched by adding water (8 mL) and shaking an additional 30 minutes. The aqueous phase was extracted with $CHCl_3$ (3 x 5 mL), and the combined extracts were washed with 2N HCl saturated with NaCl (15 mL), 10% NaCl saturated with $NaHCO_3$ (15 mL), and water (10 mL). Each wash solution was back extracted with fresh $CHCl_3$ (5 mL)

and the extract was combined with the sample. This procedure is analogous to previous work (24) in acetylating partially methylated carbohydrates. The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to approximately 0.5 mL, and analyzed by GLC (Appendix II).

SYNTHESIS AND PURIFICATION OF REAGENTS

PERMETHYLATED CELLULOSE

Dimethyl sulfate (140 mL) was added over a period of 1.5 hr to a vigorously stirred slurry of Dow Methocel (40 g) and powdered NaOH (120 g) in tetrahydrofuran (1 L). The mixture was stirred for an additional 2.5 hr, refluxed gently for 6 hr, and stirred overnight at room temperature. Benzene (473 mL) and water (400 mL) were added and the mixture was refluxed for 2 hr. The solution was poured into a flask (4 L) and the reaction vessel rinsed with water (2 x 500 mL). Upon cooling, the solution divided into two layers. The organic (top) layer was separated and the aqueous phase discarded. A portion (500 mL) of the product solution was diluted with $CHCl_3$ (500 mL) and washed with water (3 x 1 L). The washed portions were combined, dried ($CaCl_2$), and concentrated *in vacuo* until severe foaming occurred. The pastelike product was placed in a beaker and the liquid which rose to the top was periodically decanted. The permethylated cellulose was not allowed to dry completely (50 g as a thick paste), for this hindered its solubility in the next step.

2,3,6-TRI-*O*-METHYL-D-GLUCOPYRANOSE

Permethylated cellulose (50 g) was dissolved in hot (70°C) 72% sulfuric acid* (340 mL). After the cellulose had dissolved (*ca.* 3 hr), the solution was

*The acid ±0.5% was prepared using TAPPI Standard Method T13m-54.

diluted with water (3.5 L) and kept at 65°C for 18 hr. The solution was refluxed (4 hr), neutralized (NaOH), and filtered (Celite). The filtrate was reacidified with concentrated HCl (2 mL), concentrated *in vacuo* to approximately 1500 mL, and extracted with $CHCl_3$ (2 x 150 mL) to remove tetra-*O*-methyl-D-glucopyranose. The solution was concentrated to approximately 100 mL in several cycles, a cycle being the evaporation of 200-300 mL and the filtering of the precipitated Na_2SO_4. The final solution was extracted with $CHCl_3$ (4 x 200 mL), and the combined extracts were dried ($CaCl_2$) and concentrated to a sirup. Crystallization of the sirup from isopropyl ether yielded 2,3,6-tri-*O*-methyl-D-glucopyranose (15.9 g, 26.4%) as pale yellow crystals. A portion of the material was recrystallized from isopropyl ether and had m.p. 110-112°C and $[\alpha]_D$ +68.4° (c. 1.0, H_2O). Literature: m.p. 121-123°C, $[\alpha]_D$ +70.5 (H_2O) (25).

1,4-DI-*O*-ACETYL-2,3,6-TRI-*O*-METHYL-D-GLUCOPYRANOSE

2,3,6-Tri-*O*-methyl-D-glucopyranose (23 g) was dissolved in pyridine (65 mL) and acetic anhydride (80 mL). The mixture was stirred at room temperature for 23 hr, at which time TLC ($CHCl_3$:EtAc, 4:1, vol.) indicated complete conversion of the reactant. The solution was poured into ice water (450 mL) and stirred for 30 minutes. The mixture was extracted with $CHCl_3$ (6 x 100 mL) and the combined extracts were washed with 1N HCl (2 x 400 mL), saturated aq. $NaHCO_3$ (2 x 400 mL), and water (2 x 400 mL). Each wash solution was back extracted with fresh $CHCl_3$ (3 x 100 mL) and the organic phase was combined with the product solution. The combined extracts were dried ($CaCl_2$) and concentrated to yield 1,4-di-*O*-acetyl-2,3,6-tri-*O*-methyl-D-glucopyranose (31.2 g, 98.4%) as a sirup.

PHENYL 4-*O*-ACETYL-2,3,6-TRI-*O*-METHYL-1-THIO-β-D-GLUCOPYRANOSIDE

1,4-Di-*O*-acetyl-2,3,6-tri-*O*-methyl-D-glucopyranose (45 g) was dissolved in 1,2-dichloroethane (80 mL) and brominated with 32% (wt.) HBr in glacial acetic

acid (50 mL) by stirring the mixture for one hour at room temperature. The reaction solution was diluted with chloroform (300 mL) and vigorously stirred with ice and water (700 mL) for 25 minutes. The chloroform phase was separated and washed with cold water (200 mL), saturated aq. $NaHCO_3$ (200 mL), and cold water (200 mL). The solution was dried ($CaCl_2$) and concentrated to a sirup which was used in the next step.

The crude bromide sirup was dissolved in chloroform (150 mL). This solution was poured into alkaline methanol (0.5N KOH, 300 mL) which contained thiophenol (22 mL). The mixture was refluxed on a steam bath for 1.5 hr. The cooled reaction mixture was washed with water (2 x 200 mL) and 10% aq. NaOH (3 x 100 mL), dried ($CaCl_2$), and concentrated *in vacuo* to a sirup (30 g, 57.3%). A portion of the product sirup (10 g) was purified by chromatography on silica gel (Sargent-Welch, 60-200 mesh, 155 g: 25 x 1000 mm column) with chloroform:ethyl acetate (2:1, vol.). The fractions containing the pure compound were concentrated to dryness and crystallization occurred upon standing overnight (7.1 g). Two recrystallizations from isopropyl ether yielded phenyl 4-*O*-acetyl-2,3,6-tri-*O*-methyl-1-thio-β-D-glucopyranoside: m.p. 62.5-63°C, $[\alpha]_D$ -46.5° (c. 2.102, $CHCl_3$). (Found: C, 57.17%: H, 6.88%: S, 9.01%. $C_{17}H_{24}O_6S$ requires: C, 57.29%: H, 6.79%: S, 9.00%). The PMR spectrum (Fig. 11) contained a multiplet over the range of δ7.2-7.7 ppm (aromatic hydrogen), three methoxy singlets at δ3.32, 3.53, and 3.60 ppm, and the acetyl methyl singlet at δ2.01. The doublet centered at δ4.45 ppm (J 10 hz) is characteristic of an anomeric proton associated with a β-linkage (26).

1,5-ANHYDRO-2,3,6-TRI-*O*-METHYL-D-GLUCITOL

Phenyl 4-*O*-acetyl-2,3,6-tri-*O*-methyl-1-thio-β-D-glucopyranoside (10 g) was dissolved in absolute ethanol (300 mL) and Raney nickel catalyst (type W-2, 20 g)

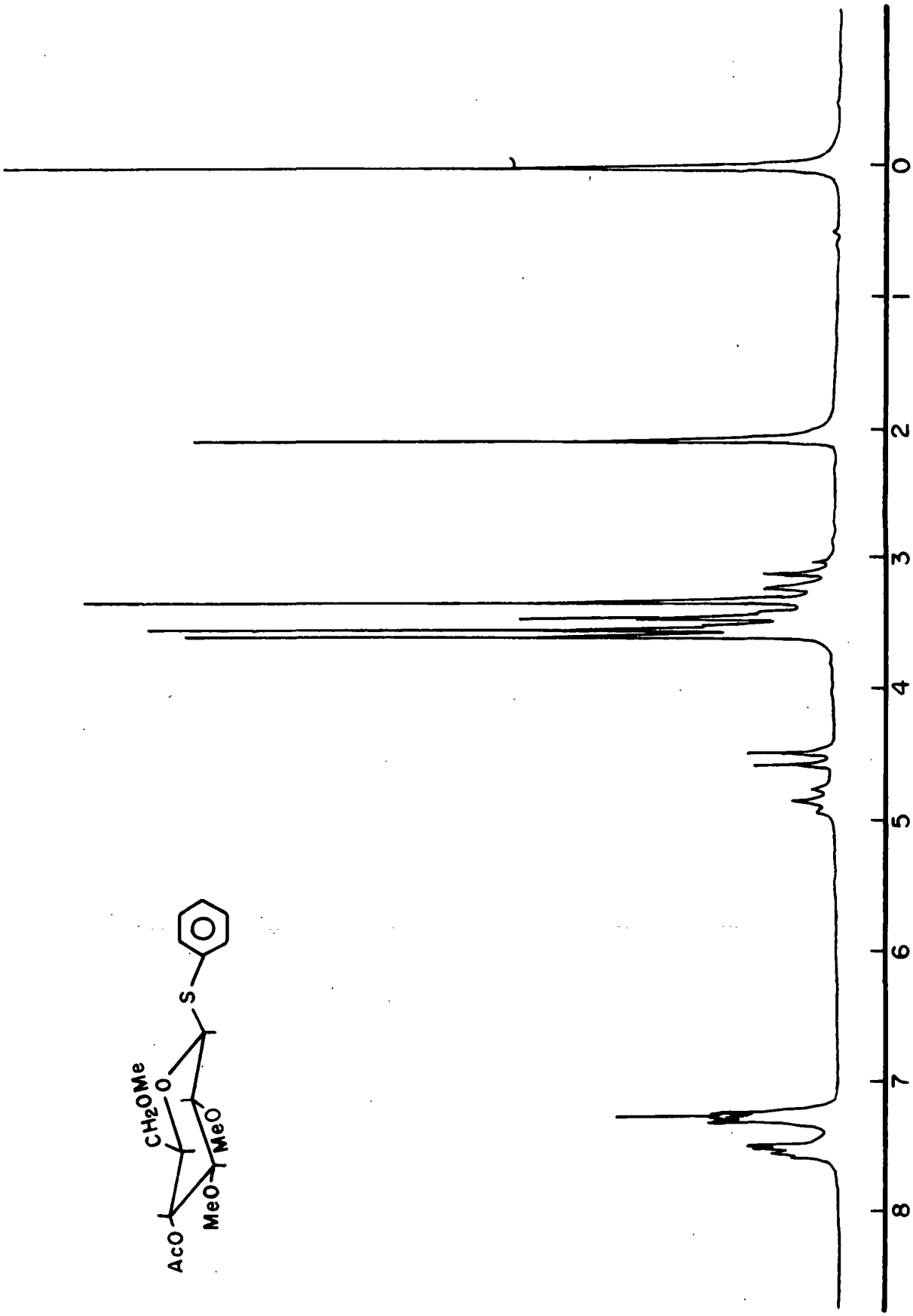


Figure 11. The PMR Spectrum of Phenyl 4-O-acetyl-2,3,6-tri-O-methyl-1-thio-β-D-glucopyranoside in $CDCl_3$

was added. The mixture was kept at approximately 50°C for 46 hr, during which time additional catalyst (5 g) was added at 4, 8, 24, and 32 hours. When TLC (Silica gel G, $CHCl_3$:EtAc, 3:1, vol.) indicated complete reaction, the mixture was cooled and the nickel was allowed to settle. The liquid was decanted and the nickel was washed with boiling EtOH (3 x 200 mL). The combined solutions were filtered (Celite) and concentrated to a sirup.

The sirup was deacetylated with sodium methoxide in methanol (27) to yield 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol as a sirup (6.0 g). The sirup was purified by chromatography on silica gel (Sargent-Welch, 60-200 mesh, 153 g: 25 x 1000 mm column) with $CHCl_3$:MeOH (15:1, vol.). The resulting sirup was further purified by vacuum distillation, yielding the pure compound as an oil (4.1 g, 61.3%) which turned to a semisolid upon refrigeration: $[\alpha]_D$ + 54.1° (c. 2.35, H_2O). Literature: m.p. 32-32.5°C, $[\alpha]_D$ + 53.8° (c. 2.43, H_2O) (4).

TETRA-O-ACETYL-α-D-GLUCOPYRANOSYL BROMIDE

This compound was prepared using the method of Bates (28). Glucose pentaacetate (200 g) was brominated with a solution of hydrogen bromide (32%, weight) in glacial acetic acid (140 mL). Crystallization of the crude bromide was accomplished by dissolving the sirup in absolute ethyl ether (300 mL) and adding petroleum ether (b.p. 30-60°C) until cloudiness developed. Refrigeration completed the crystallization yielding 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (180 g, 82.4%), m.p. 88-89°C. Literature: m.p. 88-89°C (28). This compound was stored in a vacuum desiccator over sodium hydroxide to prevent decomposition.

1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL

1,5-Anhydro-2,3,6-tri-O-methyl-D-glucitol (2 g), powdered Drierite (20 g), silver oxide (4 g), and a magnetic stirring bar were placed in an oven-dried flask (250 mL). Absolute $CHCl_3$ (90 mL) was distilled into the reaction vessel and the flask was wrapped with aluminum foil. After stirring the mixture for 30 minutes to desiccate the system, tetra-O-acetyl-α-D-glucopyranosyl bromide (8 g) and iodine (0.1 g) were added. The stirring was continued in the dark. Additional glucosyl bromide (8 g) and silver oxide (4 g) were added to the mixture at 24 and 48 hours. Periodically, samples (ca. 0.5 mL) were taken from the mixture for GLC analysis (conditions A). Prior to GLC analysis, the residual bromide in the analytical sample was hydrolyzed with silver nitrate (3% in water:acetone, 19:1, vol.) and the excess silver was precipitated by adding a saturated aqueous NaCl solution. The sample was centrifuged and the supernatant was concentrated to dryness. Chloroform (2 mL) was added to dissolve the sample for analysis. The reaction was judged to be complete when the ratio of the product disaccharide to the starting material (1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol) became constant (92 hours). The reaction mixture was filtered (Celite) and the residue was washed with $CHCl_3$ (3 x 100 mL). The combined filtrates were washed with saturated aq. $NaHCO_3$ (200 mL) and water (200 mL), dried ($CaCl_2$), and concentrated to a sirup.

The sirup was acetylated with acetic anhydride in pyridine (29). The acetylated mixture was separated by chromatography on silica gel (Sargent-Welch, 60-200 mesh, 156 g, 25 x 1000 mm column) with $CHCl_3$:EtAc (2:1, vol.). After most of the monosaccharides had been eluted (fractions monitored by GLC conditions A), the column was eluted with acetone to yield a crude disaccharide fraction. The disaccharide mixture, which was slightly contaminated with monosaccharides, was deacetylated with sodium hydroxide in methanol (27) and separated by silica gel

chromatography (Sargent-Welch, 60-200 mesh, 155 g, 25 x 1000 mm column) with $CHCl_3$:MeOH (15:1, vol.) to yield a disaccharide fraction which was TLC pure. However, GLC analysis (conditions A) of the peracetate indicated that the product was a mixture of the α and β linked disaccharides*.

The product was dissolved in 0.05N NaOH (100 mL) and heated at 80-90°C for 2.5 hours. The solution was neutralized with MB-3 resin and concentrated to dryness. Repeated passes over a silica gel column ($CHCl_3$:MeOH, 15:1, vol., 8x) yielded GLC pure 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol, which was determined by comparison of the acetate derivative with known 1,5-anhydro-2',3',4',6',-tetra-O-acetyl-2,3,6-tri-O-methyl-cellobiitol. The yield for seven Koenigs-Knorr reactions (16.2 g tri-O-methyl-D-glucitol) was 4.3 g (15.6%). The product could not be crystallized, as was previously found (4), and was isolated as an amorphous solid by drying it *in vacuo* at 60°C.

An alternate method of forming β-1,4-linkages has recently been reported (30) which claims yields on the order of 85%. 1,5-Anhydro-2,3,6-tri-O-methyl-D-glucitol (0.57 g), mercuric bromide (0.078 g), and molecular sieve (2.43 g, 4 A, powdered form) were placed in a round bottom flask (100 mL). 1,2-Dichloroethane (70 mL) was distilled into the flask. Tetra-O-acetyl-α-D-glucopyranosyl bromide (2.09 g) was added and the mixture was gently refluxed. Additional glucosyl bromide (0.5 g) was added at 24 hours, and $HgBr_2$ (0.1 g) and glucosyl bromide (0.5 g) were added at 48 hours. The reaction was monitored by TLC ($CHCl_3$:EtAc:MeOH, 8:6:1, vol.). No further reaction was observed after 100 hours. The mixture was filtered (Celite), residue was washed with 1,2-dichloroethane (3 x 50 mL), and the combined filtrates were concentrated to a sirup. Analysis of the product mixture by GLC (conditions A) indicated it was composed of the

*With this solvent the α-disaccharide was eluted first, not vice versa, as was found in earlier work (4), in which a different methanol ratio was used in the fractionation.

starting materials and approximately a 1:8 ratio of the α- to β-linked disaccharide. The yield was 0.47 g (46.1%) as the mixture of the two disaccharides. While this method resulted in a substantially higher yield than the Koenigs-Knorr reactions, the extensive purification procedures previously described would still be required.

PHENYL HEPTA-O-ACETYL-1-THIO-β-CELLOBIOSIDE

Cellobiose octaacetate (200 g) was brominated and the thiophenyl derivative was prepared as described for the preparation of phenyl 4-O-acetyl-2,3,6-tri-O-methyl-1-thio-β-D-glucopyranoside. The yield of phenyl hepta-O-acetyl-1-thio-β-cellobioside was 113 g (49.8%): m.p. 222-223°C, $[\alpha]_D$ -27.8° (c. 1.962, $CHCl_3$). Literature: m.p. 295°C (decomposition), $[\alpha]_D^{20}$ -28.5° ($CHCl_3$) (31).

PHENYL 1-THIO-β-CELLOBIOSIDE

Phenyl hepta-O-acetyl-1-thio-β-cellobioside (100 g) was deacetylated with sodium methoxide in methanol (26) to yield phenyl 1-thio-β-cellobioside (45.1 g, 62.6%): m.p. 227-230°C, $[\alpha]_D$ -50.2° (c. 1.99, H_2O). Literature: m.p. 230°C, $[\alpha]_D$ -59.2° (H_2O) (31).

PHENYL 4',6'-O-BENZYLIDENE-1-THIO-β-CELLOBIOSIDE

Phenyl 1-thio-β-cellobioside (44 g) was dissolved in benzaldehyde (150 mL), which had been dried over $CaSO_4$. Anhydrous zinc chloride (70 g) was added and the mixture was shaken for 48 hr. At that time TLC ($CHCl_3$:EtAc, 15:1, vol.) indicated no further reaction. The sirupy mixture was poured into 10% aqueous $NaHSO_3$ (2 L) and stirred for 1 hr, during which time a precipitate formed. The crude product was filtered, washed with petroleum ether (b.p. 30-60°C, 200 mL), and dried *in vacuo* to yield phenyl 4',6'-O-benzylidene-1-thio-β-cellobioside [phenyl 4-O-(4,6-O-benzylidene-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside] 34.2 g (64.4%).

A portion of the product, recrystallized (twice) from boiling absolute ethanol, had m.p. 198-199°C and $[\alpha]_D$ -65.3° (c. 0.549, CH_3OH). (Found: C, 57.59%: H, 5.58%: S, 7.18%, $C_{25}H_{30}O_{10}S$ requires: C, 57.47%: H, 5.75%: S, 6.13%). The PMR spectrum of this compound (Fig. 12) has a multiplet over the range of δ7.46-7.25 ppm (aromatic hydrogen, 10 H), indicating the two aromatic rings (thiophenyl and benzylidene groups). The portion of the spectrum in the range of δ6-3 ppm is indicative of a sugar with some free hydroxyl groups, as well as ring protons. The peaks at δ2.57 and 2.04 ppm are characteristic of the solvent, deuterated dimethyl sulfoxide. The large singlet at δ3.31 arises from an impurity (water) in the solvent.

PHENYL 4',6'-O-BENZYLIDENE-2,3,6,2',3'-PENTA-O-METHYL-1-THIO-β-CELLOBIOSIDE

Phenyl 4',6'-O-benzylidene-1-thio-β-cellobioside (32.5 g) was dissolved in tetrahydrofuran (500 mL) containing powdered NaOH (70 g). Dimethyl sulfate (50 mL) was added over a period of 1 hr to the stirred mixture. The stirring was continued for 24 hr at 40°C. The mixture was diluted with benzene (250 mL) and water (300 mL), and stirred for an additional 2 hr. The organic (top) layer was separated and concentrated to a white paste. Crystallization of the paste from isopropyl ether yielded phenyl 4',6'-O-benzylidene-2,3,6,2',3'-penta-O-methyl-1-thio-β-cellobioside [phenyl 4-O-(4,6-O-benzylidene-2,3-di-O-methyl-β-D-glucopyranosyl)-2,3,6-tri-O-methyl-1-thio-β-D-glucopyranoside] (26.4 g, 71.7%): m.p. 148-149°C, $[\alpha]_D$ -43.2° [c. 1.002, ($CHCl_3$)]. (Found: C, 60.95%: H, 6.98%: S, 5.13%. $C_{30}H_{40}O_{10}S$ requires: C, 60.95%: H, 6.77%: S, 5.41%.) The PMR spectrum of this compound (Fig. 13) also has the aromatic multiplet (10 H) over the range of δ7.49-7.23 ppm. However, upon comparison with Fig. 12 several changes in the molecule are indicated. The only peak remaining in the range of δ6-5 ppm is the singlet from the benzylidene methine proton (δ5.54 ppm). Complete methylation

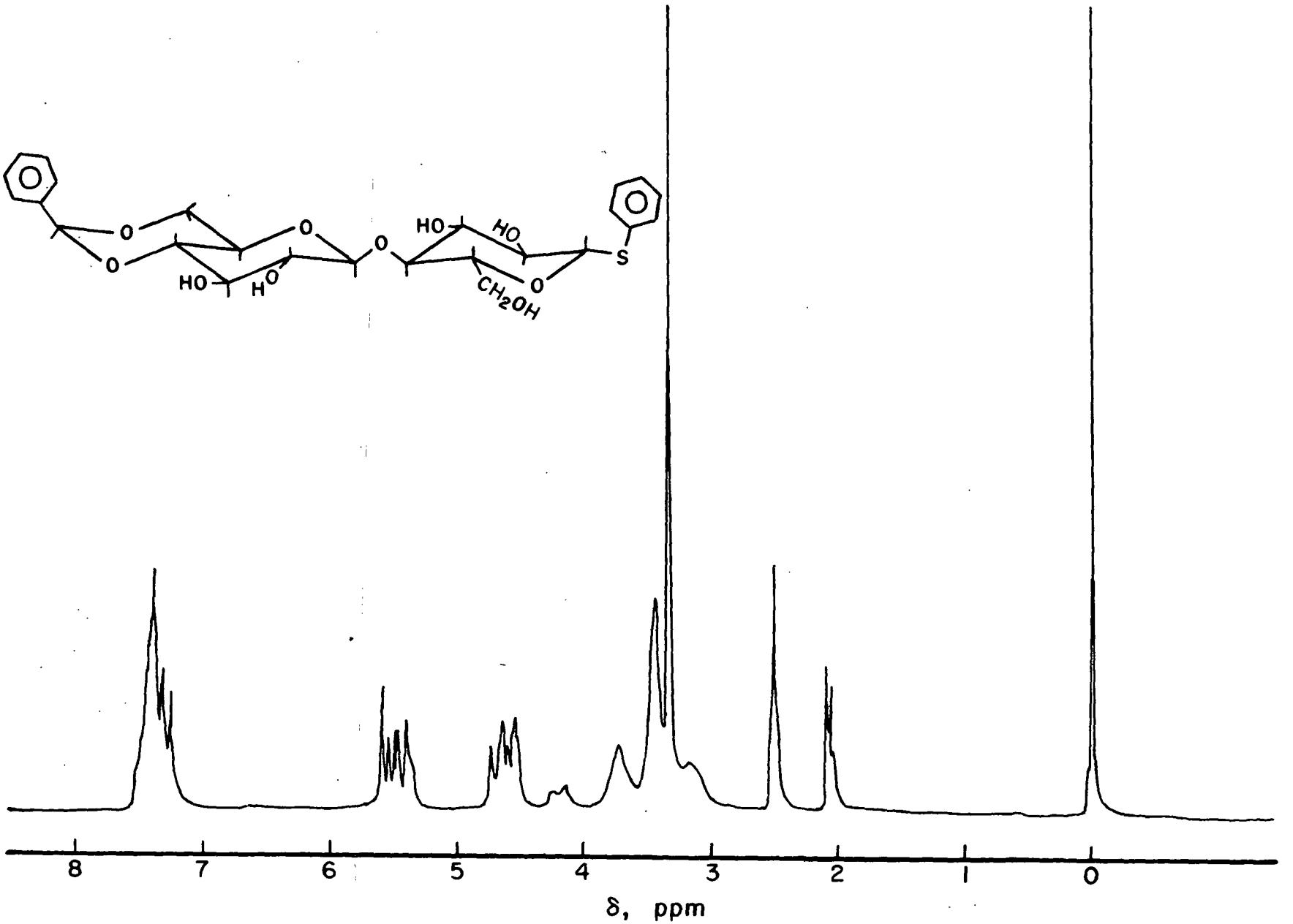


Figure 12. The PMR Spectrum of Phenyl 4',6'-O-benzylidene-1-thio-β-cellobioside in Deuterated Dimethyl Sulfoxide

of the five available hydroxyl groups is indicated by the methoxyl singlets at δ3.64, 3.60 (6 H), 3.58, and 3.40 ppm.

PHENYL 2,3,6,2',3'-PENTA-O-METHYL-1-THIO-β-CELLOBIOSIDE

Phenyl 4',6'-O-benzylidene-2,3,6,2',3'-penta-O-methyl-1-thio-β-cellobioside (22 g) was dissolved in $CHCl_3$ (100 mL) and methanol (300 mL) and IR-120 (H^+) ion exchange resin were added. The mixture was refluxed for 11 hr, at which time TLC ($CHCl_3$:MeOH, 25:1, vol.) indicated removal of the benzylidene group was complete. The mixture was cooled, and the resin was filtered and rinsed with methanol (100 mL). The combined filtrates were concentrated to a sirup. Crystallization of the sirup from isopropyl ether yielded phenyl 2,3,6,2',3'-penta-O-methyl-1-thio-β-cellobioside [phenyl 4-O-(2,3,di-O-methyl-β-D-glucopyranosyl)-2,3,6-tri-O-methyl-1-thio-β-D-glucopyranoside] (15.4 g, 82.5%) m.p. 130-131°C, $[\alpha]_D$ -34.1° (c. 1.326, $CHCl_3$). (Found: C, 54.88%: H, 7.01%: S, 6.01%. $C_{23}H_{36}O_{10}S$ requires: C, 54.75%: H, 7.14%: S, 6.35%). The PMR spectrum of this compound (Fig. 14) indicates that one of the aromatic rings of the starting material was removed as the multiplet for aromatic hydrogen (δ7.53-7.23 ppm) integrates to 5 protons. Confirmation that the benzylidene group was removed is seen in the absence of a signal from the benzylidene methine proton at δ5.54 ppm. The singlets at δ3.36, 3.60 (6 H), 3.54, and 3.38 ppm show that the methoxyl groups have been retained.

1,5-ANHYDRO-2,3,6,2',3'-PENTA-O-METHYL-CELLOBIITOL

Phenyl 2,3,6,2',3'-penta-O-methyl-1-thio-β-cellobioside (8 g) was dissolved in absolute ethanol (500 mL) and warmed to 40-45°C. Freshly prepared Raney nickel (type W-2) catalyst (30 g) was added to the solution. After 8 hr, TLC ($CHCl_3$:MeOH, 25:1, vol.) indicated the reaction was complete. The solution was filtered (Celite) and the residue was washed with hot absolute ethanol (3 x 50 mL).

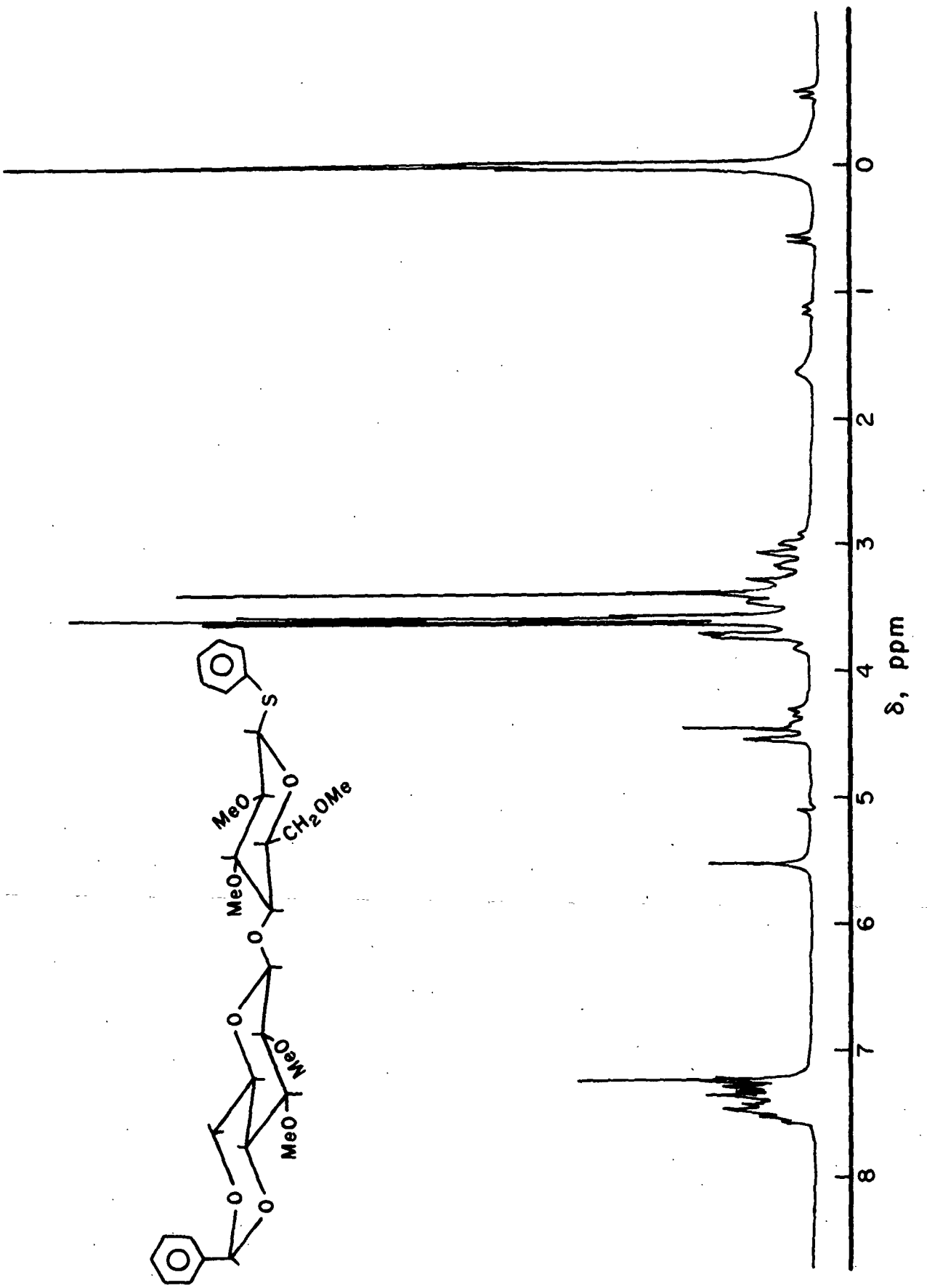


Figure 13. The PMR Spectrum of Phenyl 4',6'-O-benzylidene-2,3,6,2',3'-penta-O-methyl-1-thio-β-cellobioside in $CDCl_3$

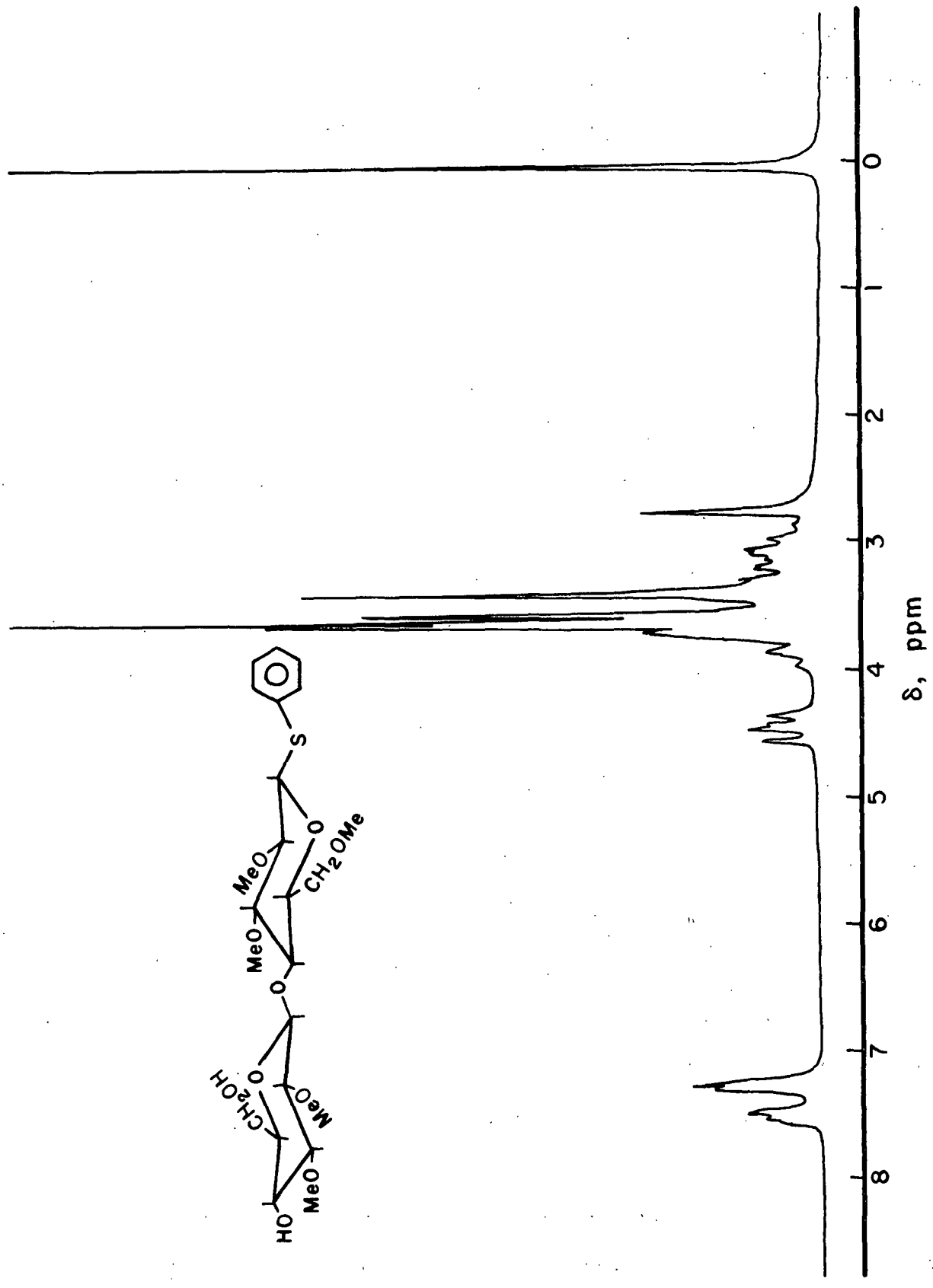


Figure 14. The PMR Spectrum of Phenyl 2,3,6,2',3'-penta-O-methyl-1-thio-β-cellobioside in $CDCl_3$

The combined filtrates were concentrated to a sirup. Three crystallizations from isopropyl ether yielded 1,5-anhydro-2,3,6,2',3'-penta-O-methyl-cellobiitol [1,5-anhydro-4-O-(2,3-di-O-methyl-β-D-glucopyranosyl)-2,3,6-tri-O-methyl-D-glucitol] (4.04 g, 64.5%): m.p. 120-121°C, $[\alpha]_D$ +29.6° (c. 1.538, H_2O). (Found: C, 51.71%: H, 8.06%: $C_{17}H_{32}O_{10}$ requires: C, 51.52%: H, 8.14%). The PMR spectrum of this compound (Fig. 15) illustrates that the aromatic moiety of the reactant has been removed. Also, the peaks at δ3.56 (6 H), 3.53, 3.43, and 3.32 demonstrate that the 5 methoxyl groups have been retained. The C-13 spectrum of the product (Fig. 16) shows the expected 17 carbon peaks, the group of 7 peaks at δ32.1-27.5 ppm, and the peak at δ46.3 ppm belong to the solvent (deuterated acetone). Peak assignments in the C-13 spectrum, made by comparison with spectra of D-glucopyranose, cellobiose, and 1,5-anhydrocellobiitol, indicate the desired 2,3,6,2',3'-penta-O-methyl-substitution pattern. The nonreducing nature of the disaccharide is evident in the absence of a pair of peaks in the δ90-100 ppm range characteristic of the α and β configurations about the C-1 carbon. The nonreducing nature of the compound was also demonstrated by a negative Fehling's test.

1,5-ANHYDRO-2,3,6-TRI-O-METHYL-D-GALACTITOL

This compound was synthesized using the method described by Morgenlie (32). 1,5-Anhydro-2,3,6-tri-O-methyl-D-glucitol (0.6 g) was dissolved in a solution of dimethyl sulfoxide (6 mL) and acetic anhydride (4 mL). The solution was allowed to stand at room temperature for 19 hr. It was then warmed to 40°C for 60 minutes and cooled. Chloroform (15 mL) was added and the solution was shaken with saturated aqueous $NaHCO_3$ (10 mL) for 1 hr. The organic layer was separated, washed with water (4 x 10 mL), dried ($CaCl_2$), and concentrated to a sirup. TLC (C_6H_6:EtOH, 10:1, vol.) of the product mixture showed three spots, two preceding and one corresponding to the starting material. The infrared spectrum of the

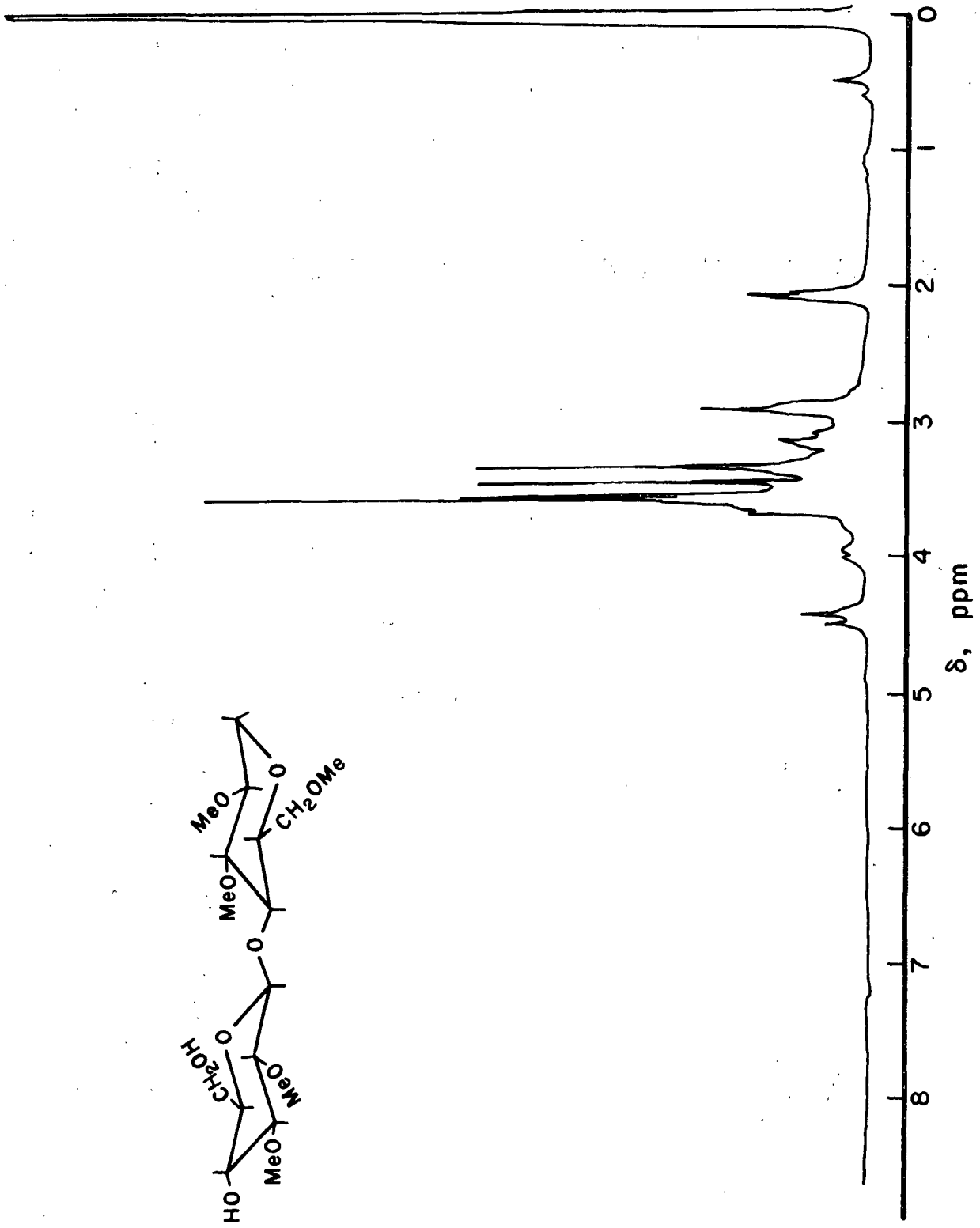


Figure 15. The PMR Spectrum of 1,5-Anhydro-2,3,6,2',3'-penta-O-methyl-cellobiitol in Deuterated Acetone

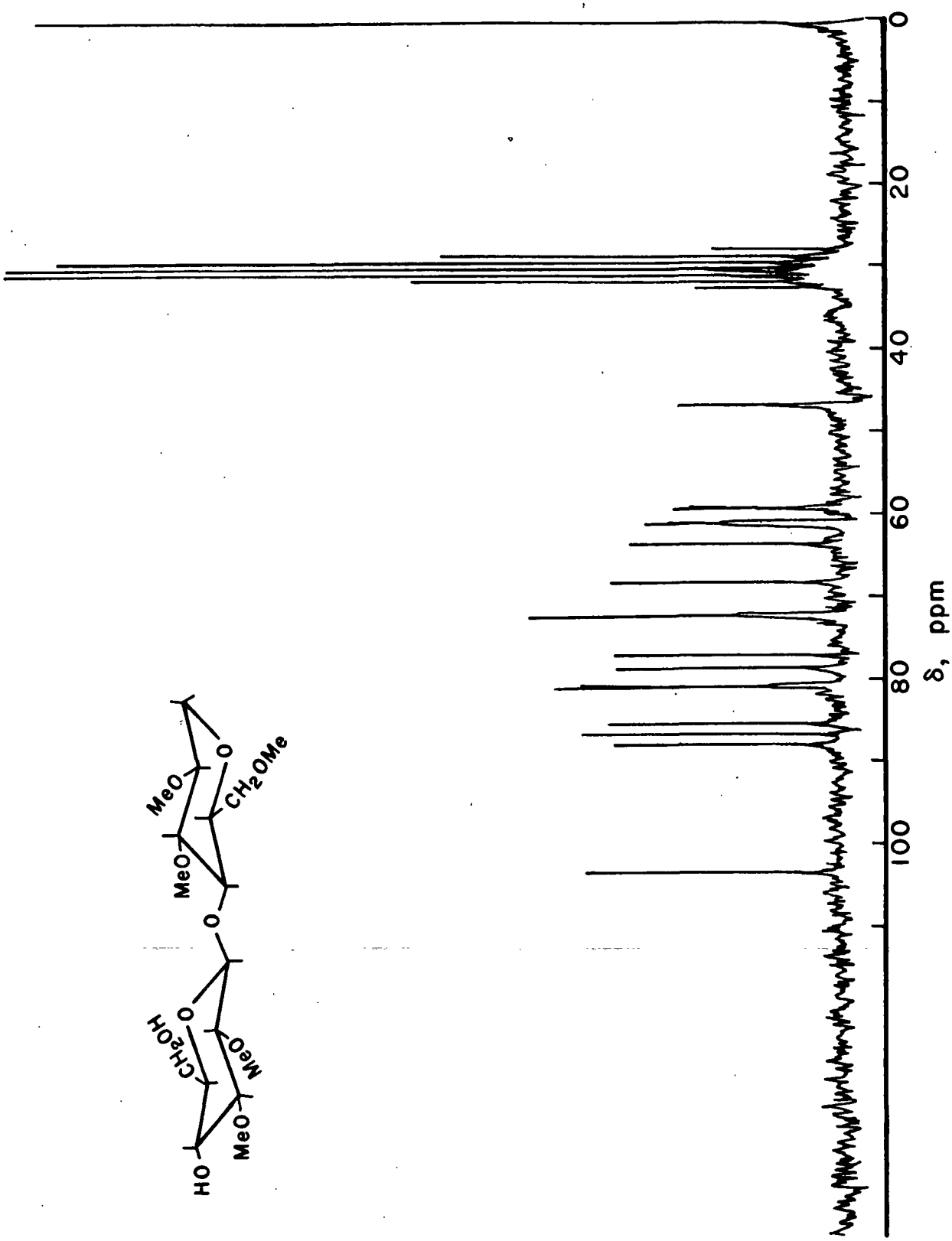


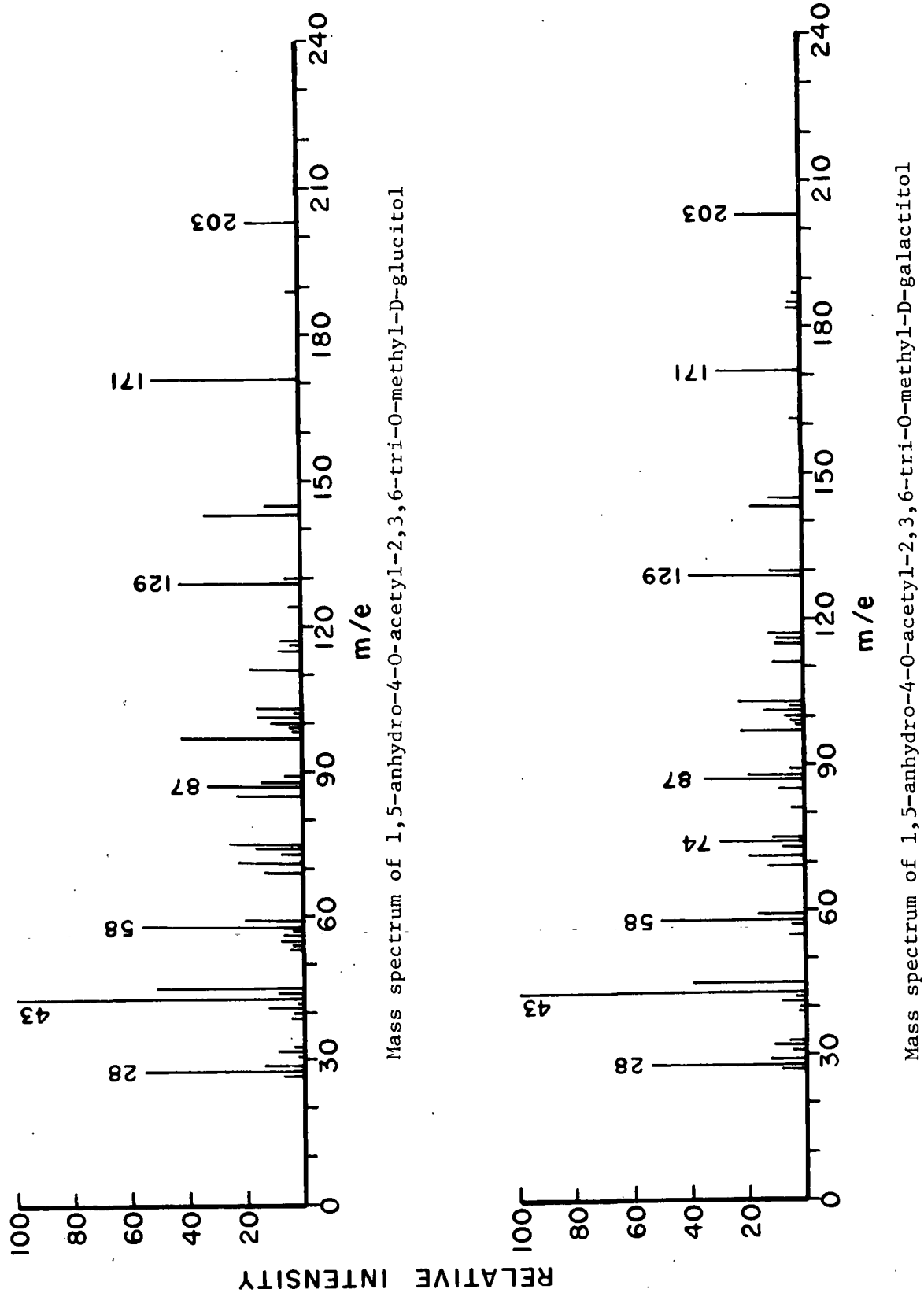
Figure 16. The C-13 Spectrum of 1,5-Anhydro-2,3,6,2',3'-penta-O-methyl-cellobiitol in Deuterated Acetone

product sirup had a strong absorption at 1740 cm^{-1}, indicating the presence of a carbonyl group. The product sirup was freeze dried yielding a powder (0.508 g).

The powder was dissolved in a 0.049M sodium borate decahydrate solution (10 mL) and reacted with sodium borohydride (0.5 g) for 2 hr. The reaction solution was neutralized with IR-120 (H^+) resin, filtered, concentrated to a sirup, and reconcentrated from methanol (2 x 25 mL). A sample of the product was acetylated for GLC analysis (conditions B). Peak (IV) of the chromatogram (Fig. 9) was identified as 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol by injection of the known compound. If peak (VIII) was 1,5-anhydro-2,3,6-tri-O-methyl-D-galactitol its mass spectrum should be similar to that of 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol, since the only structural difference in the two epimers is the configuration at C-4. The match of the mass spectrum of peak (VIII) to that obtained for 1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol (Fig. 17) confirms it as 1,5-anhydro-2,3,6-tri-O-methyl-D-galactitol.

CYCLOHEXYL β-CELLOBIOSIDE

Hepta-O-acetyl-α-cellobiosyl bromide was condensed with cyclohexanol in a modified Koenigs-Knorr reaction using mercury salts as catalysts (33). Drierite (10-20 mesh, 40 g), yellow mercuric oxide (13.5 g), mercuric bromide (1.0 g), and anhydrous cyclohexanol (60 mL) were added to absolute $CHCl_3$ (300 mL). The mixture was stirred for 30 minutes to desiccate the system. Hepta-O-acetyl-α-cellobiosyl bromide (44 g) was added to the mixture and the stirring was continued, in the dark, for a total of 10 hr. The slurry was filtered (Celite) into 20% aq. potassium iodide (300 mL) and the residue was rinsed with $CHCl_3$ (100 mL). The organic layer was separated, washed with 20% aq. potassium iodide (3 x 200 mL) and water (500 mL), dried ($CaCl_2$), and concentrated to a sirup.



Mass spectrum of 1,5-anhydro-4-O-acetyl-2,3,6-tri-O-methyl-D-glucitol

Mass spectrum of 1,5-anhydro-4-O-acetyl-2,3,6-tri-O-methyl-D-galactitol

Figure 17. Comparison of the Mass Spectra of 1,5-Anhydro-4-O-acetyl-2,3,6-tri-O-methyl-D-glucitol and 1,5-Anhydro-4-O-acetyl-2,3,6-tri-O-methyl-D-galactitol

Three crystallizations from absolute ethanol afforded cyclohexyl hepta-O-acetyl-β-cellobioside (23.4 g, 52%): m.p. 201-203°C, $[\alpha]_D$ -21.3° (c. 1.856, $CHCl_3$). Literature: m.p. 202-203°C, $[\alpha]_D$ -25.7° (c. 3.928, $CHCl_3$) (4).

Cyclohexyl hepta-O-acetyl-β-cellobioside (20 g) was deacetylated with sodium methoxide in methanol (27). Two crystallizations from absolute ethanol yielded cyclohexyl β-cellobioside (8.5 g, 72%): m.p. 207-208°C, $[\alpha]_D$ -24.9° (c. 1.052, H_2O). Literature: m.p. 206-207°C, $[\alpha]_D$ -26.3° (c. 2.66, H_2O) (4).

n-PROPYL β-D-XYLOPYRANOSIDE

A quantity of this material sufficient for completing this study was graciously supplied by Dr. L. R. Schroeder.

RANEY NICKEL TYPE W-2 CATALYST

This material was prepared along the guidelines of Monzingo (34). A sodium hydroxide solution (380 g in 1.5 L H_2O) was placed in a beaker (4 L). The alloy (50-50 Ni-Al, 300 g) was added at such a rate that the foaming of the solution did not rise above the 3 L mark on the flask. This was accomplished by adding a small amount (2-3 g) of the alloy and stirring the mixture with a glass rod until the foaming subsided. All the alloy had been added after 4 hr, at which time the beaker was placed on a steam bath until the evolution of hydrogen ceased (8-16 hr). After cooling, the liquid was decanted. The nickel was slurried with water, allowed to settle, and the liquid was decanted. The nickel was slurried with a second sodium hydroxide solution (50 g in 500 mL H_2O), allowed to settle and the liquid was decanted. The catalyst was washed free of base by repeating the cycle of dispersing in fresh water and decanting. The pH of the wash solution was approximately 7 after 20-30 washings. The water was exchanged for ethanol by repeating the washing procedure with 95% ethanol

(3 x 500 mL) and then absolute ethanol (3 x 500 mL). The Raney nickel (ca. 150 g) was stored in a tightly capped container under ethanol until needed. The efficiency of the catalyst depended on its freshness. Consequently, it was used within several days of manufacture.

ACKNOWLEDGMENT

The author wishes to acknowledge the personal guidance and assistance of the chairman of his thesis advisory committee, Dr. Leland R. Schroeder, whose contributions toward the successful completion of this work cannot be quantified.

In addition I would like to thank Mr. John Rademacher and Mr. John Gast for their help in obtaining and interpreting the NMR spectra.

I also wish to express my appreciation to my family, and especially to my wife, Debbie, for their unfailing support during the course of this study.

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APPENDIX I

CALCULATION OF THERMODYNAMIC FUNCTIONS OF ACTIVATION

The Arrhenius activation energy, E_a, was determined by using the logarithmic form of the Arrhenius equation [Eq. (23)]:

$$\ln k_{obs} = -E_a/RT + \ln A \tag{23}$$

where k_{obs} = the pseudo-first-order rate constant,

R = universal gas constant, 1.987 cal/°K-mole,

A = empirical frequency factor,

and T = temperature, °K.

Figure 18 is a plot of the data for the Arrhenius equation of glucosyl-oxygen bond cleavage in 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol (measured by k_g). The slope of the line ($-E_a/R$) was evaluated by the method of least squares.

The enthalpy of activation ($\Delta H^{\ddagger}$) was calculated from Eq. (24), in which it is assumed that $\Delta V^{\ddagger}$, the volume change in the reaction, was negligible.

$$\Delta H^{\ddagger} = E_a - RT + P\Delta V^{\ddagger} \tag{24}$$

From the theory of absolute reaction rates (35) Eq. (25) relates the rate constant to the entropy of activation ($\Delta S^{\ddagger}$):

$$k_{obs} = (ekT/h) \cdot (e^{-E_a/RT}) \cdot (e^{\Delta S^{\ddagger}/R}) \tag{25}$$

where e = the base for Napierian logarithms, 2.7183,

k = Boltzmann's constant, 1.38×10^{-16} erg/°K,

and h = Planck's constant, 6.625×10^{-27} erg·sec.

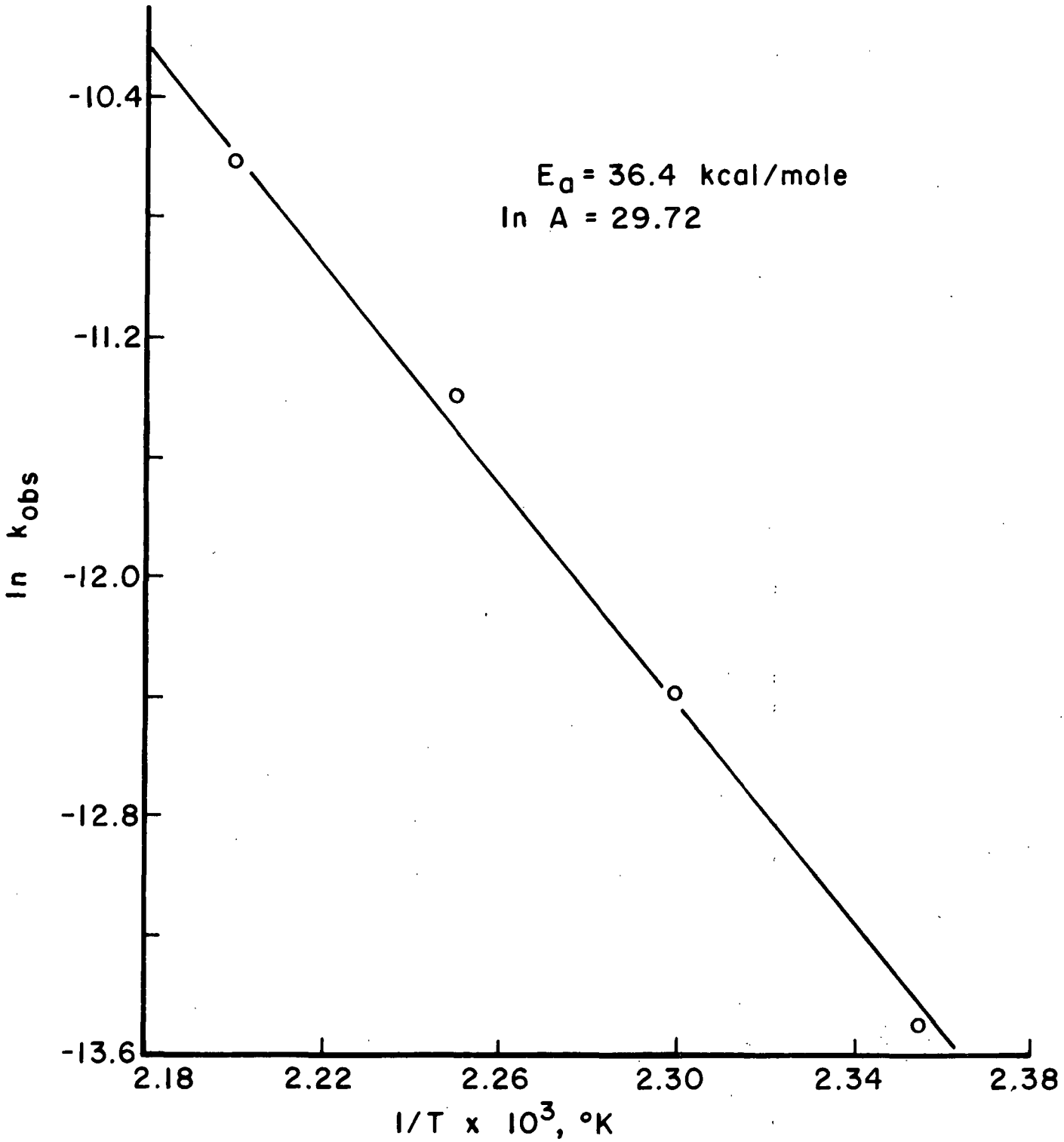

Figure 18. Arrhenius Correlation for the Degradation of the Glucosyl-oxygen Bond of 1,5-Anhydro-2,3,6-tri-O-methyl Cellobiitol in 2.5N Sodium Hydroxide

Substitution of Eq. (25) into Eq. (23) and rearrangement yields an expression for the entropy of activation, Eq. (26).

$$\Delta S^{\ddagger} = R \ln(A/T) + R \ln(h/ek) \qquad (26)$$

APPENDIX II

GAS-LIQUID CHROMATOGRAPHY

The response factors of the various compounds utilized in the course of this study were determined by GLC analysis of acetylated samples in which the molar ratio of the compound to its internal standard were known and Eq. (18):

$$F_x = A_r M_r \tag{18}$$

where F_x = response factor for compound X, relative to its internal standard,

A_r = peak area ratio of the internal standard to X (IS/X),

M_r = molar ratio of compound X to its internal standard ([X]/[IS]).

Table IX lists the GLC conditions used, while Table X gives the retention times and response factors for the compounds encountered in this work.

TABLE IX

GLC OPERATING CONDITIONS[a]

Conditions	A	B	C
Injector temp. °C	250	250	250
Detector temp. °C	325	320	320
Nitrogen flow (mL/min)	60	20	30
Column temp. °C	120-295 at 8°/min	140 for 10 min then to 160 at 4°/min	240 for 10 min then to 290 at 6°/min

[a] In all cases the column was stainless steel (5 ft x 0.125 inch) packed with 10% SE-30 on 60/80 mesh DMCS-AW Chromosorb W.

APPENDIX II (Continued)

GAS-LIQUID CHROMATOGRAPHY

TABLE X

GLC RESPONSE FACTORS AND RETENTION TIMES OF THE COMPOUNDS

Conditions	Compound, acetate derivative of	Retention Time, minutes	F_x
B	1,5-Anhydro-2,3,6-tri-O-methyl-D-galactitol	6.0	Not Determined
B	1,5-Anhydro-2,3,6-tri-O-methyl-D-glucitol (IV)	7.2	1.615[a]
B	1,6-Anhydro-β-D-glucopyranose (I)	15.6	1.454[a]
B	n-Propyl β-D-xylopyranoside (XIII)	18.9	1.000
C	1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol (III)	7.5	1.528[b]
C	1,5-Anhydro-2,3,6,2',3'-penta-O-methyl-cellobiitol	7.7	1.076[b]
C	Cyclohexyl β-cellobioside (XIV)	21.6	1.000

[a] Based on (XIII).
[b] Based on (XIV).

Figure 19 is a sample chromatogram of the analysis for the monosaccharides (Conditions B).

Figure 20 is a sample chromatogram for the determination of 1,5-anhydro-2,3,6-tri-O-methyl-cellobiitol (Conditions C).

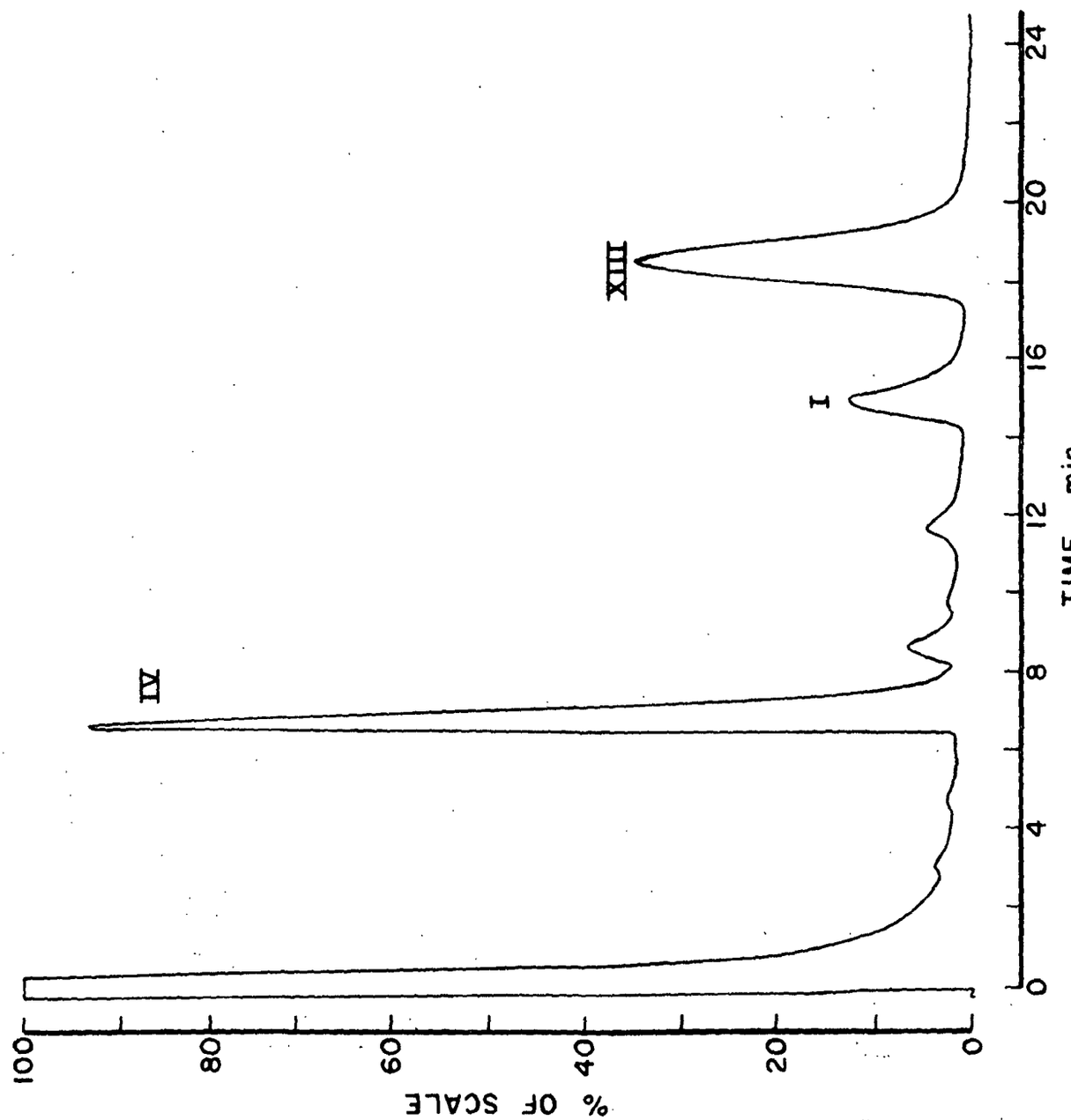

Figure 19. Sample Chromatogram of the Monosaccharides

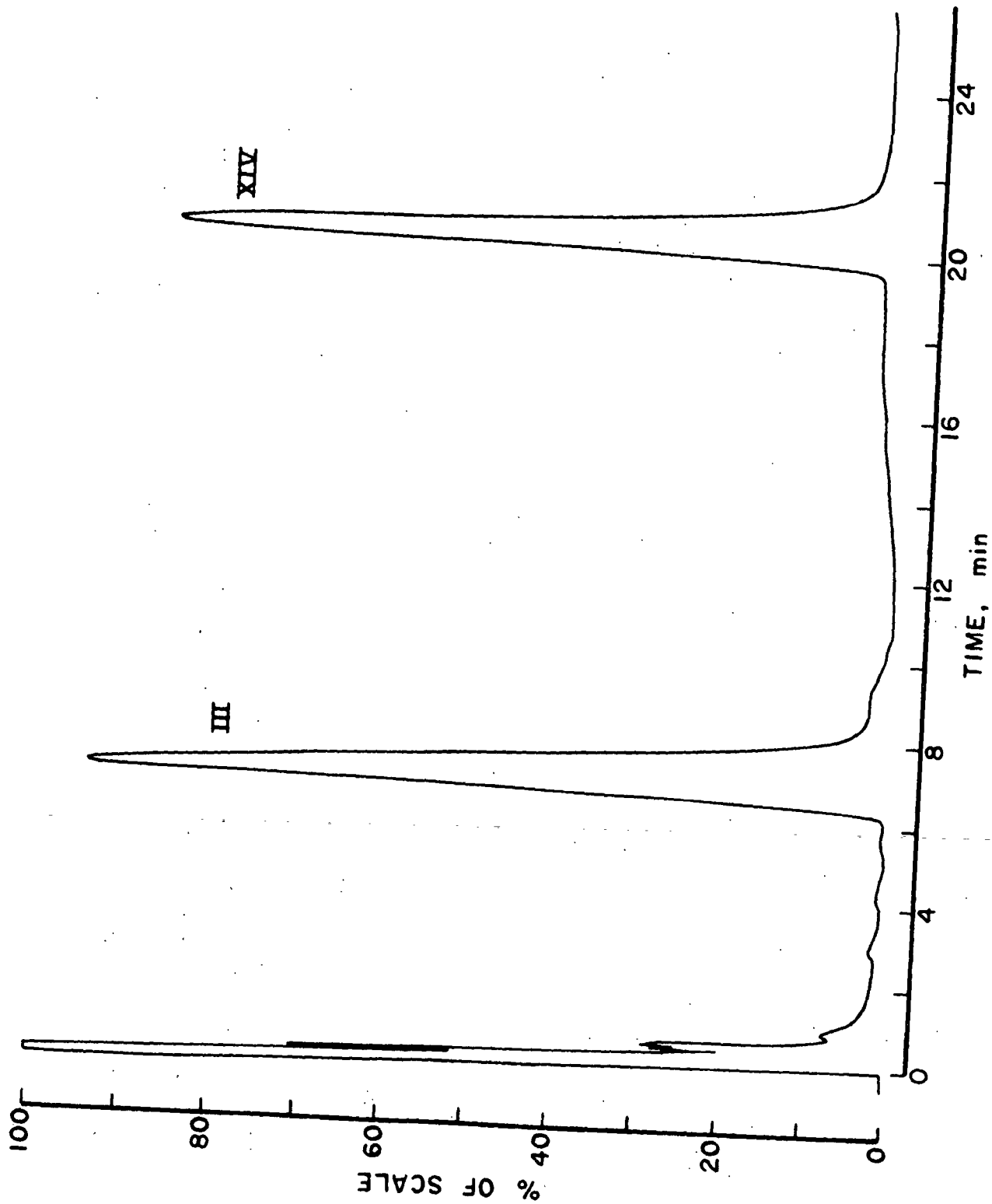

Figure 20. Sample Chromatogram of the Analysis of 1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol

APPENDIX III

EXPERIMENTAL DATA

TABLE XI

DEGRADATION OF 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL (0.01M) IN 2.497N SODIUM HYDROXIDE AT 151.4°C ± 0.1°C

Time minutes,	1,6-Anhydro-β-D-gluco-pyranose, 10^3 mole/L	1,5-Anhydro-2,3,6-tri-O-methyl-D-glucitol, 10^3 mole/L	1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol, 10^3 mole/L
0.6	0.0	0.0	9.77
2	0.0229	0.120	9.69
3	0.0	0.0	11.1
550	0.241	0.433	9.05
551	0.237	0.430	8.63
1300	0.411	0.969	8.13
1301	0.306	0.968	9.34
2000	0.477	1.64	7.75
2001	0.456	1.53	8.16
2700	0.426	2.09	7.27
2701	0.348	2.04	7.87
3400	0.387	2.02	6.77
3401	0.431	2.35	6.85
4200	0.384	2.81	6.55
4201	0.278	3.32	7.02
4800	0.314	3.06	5.90
5700	--	3.46	5.45

$$k_1 = 1.05 \times 10^{-6} \text{ sec.}^{-1}$$

$$k_g = 1.38 \times 10^{-6} \text{ sec.}^{-1}$$

$$k_r = 1.64 \times 10^{-6} \text{ sec.}^{-1}$$

APPENDIX III (Continued)

EXPERIMENTAL DATA

TABLE XII

DEGRADATION OF 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL (0.01M) IN 2.490N SODIUM HYDROXIDE AT 161.9°C ± 0.15°C

Time, minutes	1,6-Anhydro-β-D-gluco-pyranose, 10^3 mole/L	1,5-Anhydro-2,3,6-tri-O-methyl-D-glucitol, 10^3 mole/L	1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol, 10^3 mole/L
0	0.0444	0.0532	9.52
50	0.114	0.149	9.46
101	0.259	--	9.46
200	0.259	0.459	8.90
300	0.333	0.643	8.87
451	0.342	0.786	--
600	0.470	1.32	8.19
1250	0.427	2.55	6.77
2800	--	4.59	4.40

$k_1 = 2.72 \times 10^{-6}$ sec^{-1}

$k_g = 4.10 \times 10^{-6}$ sec^{-1}

$k_r = 4.65 \times 10^{-6}$ sec^{-1}

APPENDIX III (Continued)

EXPERIMENTAL DATA

TABLE XIII

DEGRADATION OF 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL (0.01M) IN 2.482N SODIUM HYDROXIDE AT 171.4°C ± 0.1°C

Time, minutes	1,6-Anhydro-β-D-gluco-pyranose, 10^3 mole/L	1,5-Anhydro-2,3,6-tri-O-methyl-D-glucitol, 10^3 mole/L	1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol, 10^3 mole/L
0	0.0650	0.0862	10.3
26	0.136	0.188	10.2
27	0.0699	0.150	10.1
50	0.181	0.319	10.3
51	0.108	0.238	10.7
100	0.299	0.319	9.01
101	0.181	0.238	--
150	0.372	0.892	8.94
230	0.483	1.73	8.55
231	0.310	1.54	--
440	0.457	2.74	7.34
715	0.337	3.77	5.99
716	--	--	6.03
1300	--	5.58	4.25

$k_1 = 6.43 \times 10^{-6}$ sec^{-1}

$k_g = 10.9 \times 10^{-6}$ sec^{-1}

$k_r = 11.8 \times 10^{-6}$ sec^{-1}

APPENDIX III (Continued)

EXPERIMENTAL DATA

TABLE XIV

DEGRADATION OF 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL (0.01M) IN 2.482N SODIUM HYDROXIDE AT 171.2°C ± 0.1°C

Time, minutes	1,6-Anhydro-β-D-gluco-pyranose, 10^3 mole/L	1,5-Anhydro-2,3,6-tri-O-methyl-D-glucitol, 10^3 mole/L	1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol, 10^3 mole/L
0	0.0192	0.0220	10.2
1	0.0241	0.0287	9.33
25	0.0762	0.138	9.35
50	0.117	0.249	9.74
75	0.197	0.412	9.05
100	0.174	0.425	--
101	0.277	0.598	9.29
200	0.314	0.906	8.62
390	0.356	1.42	7.18
390	0.389	1.15	7.38
695	--	2.91	5.77
1290	--	6.31	3.88

$k_1 = 5.59 \times 10^{-6}$ sec^{-1}

$k_g = 11.6 \times 10^{-6}$ sec^{-1}

$k_r = 12.1 \times 10^{-6}$ sec^{-1}

APPENDIX III (Continued)

EXPERIMENTAL DATA

TABLE XV

DEGRADATION OF 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL (0.01M) IN 2.483N SODIUM HYDROXIDE AT 182.1°C ± 0.1°C

Time, minutes	1,6-Anhydro-β-D-gluco-pyranose, 10^3 mole/L	1,5-Anhydro-2,3,6-tri-O-methyl-D-glucitol, 10^3 mole/L	1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol, 10^3 mole/L
0	0.0713	0.151	11.3
1	0.0774	0.148	10.7
20	0.152	0.305	10.7
21	0.221	0.516	11.0
42	0.296	0.780	10.2
43	0.311	0.870	10.5
60	0.276	0.884	9.91
61	0.337	1.13	10.5
90	0.397	1.53	9.57
91	0.421	1.61	9.70
120	0.450	2.14	8.99
121	0.447	1.93	9.15
215	0.424	3.63	7.84
216	0.405	2.42	7.26
370	--	5.65	6.48
371	--	5.09	5.26
670	--	--	3.76
671	--	6.64	3.17

$$k_1 = 12.6 \times 10^{-6} \text{ sec}^{-1}$$

$$k_g = 24.4 \times 10^{-6} \text{ sec}^{-1}$$

$$k_r = 26.4 \times 10^{-6} \text{ sec}^{-1}$$

APPENDIX III (Continued)

EXPERIMENTAL DATA

TABLE XVI

DEGRADATION OF 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL (0.01M) IN 0.4749N SODIUM HYDROXIDE AT 171.3°C ± 0.1°C

Time, minutes	1,6-Anhydro-β-D-gluco-pyranose, 10^3 mole/L	1,5-Anhydro-2,3,6-tri-O-methyl-D-glucitol, 10^3 mole/L	1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol, 10^3 mole/L
0	0.0199	0.0278	10.3
1	0.0227	0.0323	10.6
53	0.0661	0.116	10.0
100	0.128	0.208	9.70
150	0.245	0.375	9.75
151	0.160	0.278	9.70
200	0.280	0.485	9.71
350	0.387	0.720	9.24
351	0.355	0.563	9.20
690	0.487	1.47	8.86
1263	0.487	2.38	7.47
1800	0.415	2.72	6.25

$$k_1 = 2.30 \times 10^{-6} \text{ sec}^{-1}$$

$$k_g = 3.43 \times 10^{-6} \text{ sec}^{-1}$$

$$k_r = 4.30 \times 10^{-6} \text{ sec}^{-1}$$

APPENDIX III (Continued)

EXPERIMENTAL DATA

TABLE XVII

DEGRADATION OF 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL (0.01M) IN 0.5N SODIUM HYDROXIDE AND 2.0M SODIUM TOSYLATE AT 171.6°C ± 0.2°C

Time, minutes	1,6-Anhydro-β-D-gluco-pyranose, 10^3 mole/L	1,5-Anhydro-2,3,6-tri-O-methyl-D-glucitol, 10^3 mole/L	1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol, 10^3 mole/L
0	0.0208	0.0196	--
1	0.0173	0.0172	10.0
107	0.149	0.137	9.73
200	0.237	0.256	--
300	0.288	0.351	8.99
301	0.266	0.333	9.28
400	0.357	0.469	--
606	0.496	0.833	8.68
798	0.554	1.06	8.67
799	0.577	1.08	--
1300	0.641	1.81	7.74
1820	0.622	2.58	6.81

$$k_1 = 2.32 \times 10^{-6} \text{ sec}^{-1}$$

$$k_g = 2.76 \times 10^{-6} \text{ sec}^{-1}$$

$$k_r = 3.30 \times 10^{-6} \text{ sec}^{-1}$$

APPENDIX III (Continued)

EXPERIMENTAL DATA

TABLE XVIII

DEGRADATION OF 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL (0.01M) IN 0.75N SODIUM HYDROXIDE AND 1.75M SODIUM TOSYLATE AT 171.2°C ± 0.1°C

Time, minutes	1,6-Anhydro-β-D-gluco-pyranose, 10^3 mole/L	1,5-Anhydro-2,3,6-tri-O-methyl-D-glucitol, 10^3 mole/L	1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol, 10^3 mole/L
0	0.0426	0.0632	10.6
1	0.0538	--	10.7
61	0.139	0.139	10.5
260	0.416	0.588	9.90
370	0.468	0.936	--
371	--	0.989	9.62
512	0.544	1.22	9.32
1000	0.630	2.12	8.13
1300	0.628	--	7.71
1301	0.601	2.71	7.35
1551	0.613	--	6.99
1800	0.577	3.56	6.57

$k_1 = 2.95 \times 10^{-6}$ sec^{-1}

$k_g = 3.83 \times 10^{-6}$ sec^{-1}

$k_r = 4.47 \times 10^{-6}$ sec^{-1}

APPENDIX III (Continued)

EXPERIMENTAL DATA

TABLE XIX

DEGRADATION OF 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-CELLOBIITOL (0.01M) IN 1.5N SODIUM HYDROXIDE AND 1.0M SODIUM TOSYLATE AT 170.8°C ± 0.1°C

Time, minutes	1,6-Anhydro-β-D-gluco-pyranose, 10^3 mole/L	1,5-Anhydro-2,3,6-tri-O-methyl-D-glucitol, 10^3 mole/L	1,5-Anhydro-2,3,6-tri-O-methyl-cellobiitol, 10^3 mole/L
0	0.0172	0.0243	8.63
75	0.107	0.132	--
76	0.115	0.140	8.28
180	0.215	0.376	--
225	0.222	0.436	7.53
300	0.226	0.618	--
301	0.255	0.728	6.50
445	0.436	1.11	6.73
600	0.349	1.62	6.99
825	0.390	2.01	6.69
826	0.385	1.92	6.39
1400	--	3.26	5.18

$k_1 = 3.53 \times 10^{-6}$ sec^{-1}

$k_g = 5.80 \times 10^{-6}$ sec^{-1}

$k_r = 5.99 \times 10^{-6}$ sec^{-1}

APPENDIX III (Continued)

EXPERIMENTAL DATA

TABLE XX

DEGRADATION OF 1,5-ANHYDRO-2,3,6,2',3'-PENTA-O-METHYL-CELLOBIITOL (0.01M) IN 2.485N SODIUM HYDROXIDE AT 71.4°C ± 0.1°C

Time, minutes	1,5-Anhydro-2,3,6-tri-O-methyl-D-glucitol 10^3 mole/L	1,5-Anhydro-2,3,6,2',3'-penta-O-methyl-cellobiitol 10^3 mole/L
0	0.0	9.69
470[a]		9.18
1240		9.20
1600[a]		8.75
2000		8.48
2700		8.08
2701	0.389	7.93
3400	0.516	--
4300	0.640	7.64
5000	0.586	7.15
6300	0.914	6.63
6301	0.985	6.50

$k_g = 3.22 \times 10^{-7}$ sec^{-1}

$k_r = 9.95 \times 10^{-7}$ sec^{-1}

[a]Average of duplicate determinations.

APPENDIX III (Continued)

EXPERIMENTAL DATA

TABLE XXI

THE STABILITY OF 1,5-ANHYDRO-2,3,6-TRI-O-METHYL-D-GLUCITOL (0.006M) IN 2.514N SODIUM HYDROXIDE AT 171.2°C ± 0.2°C

Time, minutes	1,5-Anhydro-2,3,6-tri-O-methyl-D-glucitol 10^3 mole/L
4645	6.03
4647	6.06
8585	5.00
10211	6.13
14726	5.07
16391	5.78
From the combined purged samples	5.87